EXHIBIT 3

REPORT OF T.W. SADLER, Ph.D

Report on M[redacted] G[redacted] by T.W. Sadler, Ph.D

I have been retained by counsel to render an expert opinion regarding: (1) the role that serotonin (5-HT) plays in the embryonic development of the heart and major vessels(2) how maternal exposure to selective serotonin reuptake inhibitors (SSRIs) like Zoloft (sertraline) can alter embryonic development of the heart and major vessels; and (3) how Zoloft caused or contributed to the cardiovascular birth defects in M[redacted] G[redacted].

I. Qualifications

I am an embryologist/developmental biologist/ teratologist who has worked in the field for over 40 years. I received a Ph.D. in Anatomy and Embryology from the University of Virginia in 1976. From 1976 to 1982, I taught Anatomy and Cell Biology, first at the University of Virginia School of Medicine and then the University of Cincinnati College of Medicine. From 1982-2002, I taught the same subjects at the University of North Carolina in Chapel Hill.

I conducted research in embryology and the origin of birth defects in humans (primarily neural tube defects) from 1973 to 2002 and spent most of my career at the University of North Carolina, Chapel Hill where I became a Full Professor in 1988. I was Co-Chair and Founder of the North Carolina Folic Acid Council and Co-Chair and Founder of the Council for Prevention of Neural Tube Defects in North Carolina, which established a Folic Acid Program and Active Birth Defects Registry for all children born in the state. I also Founded and Directed the Birth Defects Center at the University of North Carolina in 1992 whose mission was to discover the causes and means to prevent birth defects in humans.

This mission was a reflection of my personal research using animal models to study the origins and ways for prevention of birth defects related to human exposures, such as maternal diabetes and a variety of teratogens, including Selective Serotonin Reuptake Inhibitors (SSRIs), hyperthermia, hypoglycemia, cocaine, alcohol, and others. Most of these studies focused on the effects of these exposures on neural tube development to provide basic information on the origin

of neural tube defects, including spina bifida and anencephaly. Together with the March of Dimes, I worked to establish birth defects prevention strategies and programs throughout the United States. An additional program I assisted with was the establishment of active birth defects registries in different states for conducting epidemiological studies on the origin of congenital malformations in humans. During this time, I was one of the first scientists to study the role that serotonin plays in embryonic development during early stages involving neurulation, craniofacial, and cardiac morphogenesis. In addition to the published studies, my colleagues and I presented papers at scientific meetings regarding the origin and causes of neural tube and other defects and the role of serotonin in embryonic development, including how alterations in serotonin concentrations can and do impact the developing embryo resulting in congenital malformations.

My professional experience includes being Editor of the journal *Teratology* and a member of the Human Embryology and Development Study Section at the National Institutes of Health. In 2002, I received the Godfrey P. Oakley, Jr. Award from the National Birth Defects Prevention Network for my significant contributions to the field of birth defects in humans.

I am an expert in embryology, including human development. I have over 200 related publications, including articles, abstracts and books. I have been the author of the medical textbook, *Langman's Medical Embryology* for over 30 years. *Langman's Medical Embryology Langman's Medical Embryology* is a medical textbook explaining human embryology and development and the origins of birth defects in humans. This medical textbook about human embryology is in its 13th edition, having been first published in 1969, and has been translated into 12 different languages and is used throughout the United States and the world. Thus, throughout my career, I have been involved in analyzing and teaching about the origin and prevention of birth defects in humans from my work in the laboratory to evaluating human teratogens to writing and lecturing about these topics to explaining to parents how and why birth defects occur in their children.

Currently, I am an Adjunct Professor of Pediatrics at the University of Utah, Visiting Professor of Cell Biology and Anatomy at the Quillen College of Medicine at East Tennessee State University, Senior Scholar at the Greenwood Genetics Center in Greenwood, SC and a Consultant in Embryology and Birth Defects Prevention, giving lectures and assisting states with their birth defect prevention campaigns. I have also been asked over the years to talk with

parents and healthcare providers about the origins and risk factors for birth defects in children. While my career has included whole animal and in vitro research techniques, the sum and substance of my life's work has been the application and use of this research in preventing birth defects in human beings and communicating risk factors and mechanisms of how birth defects occur in humans to parents and healthcare providers.

II. Methodology

In formulating my opinions in this case, I gathered, considered, and analyzed materials and data, which are the type and substance that embryologists and teratologists reasonably utilize and rely upon when conducting this type of analysis, including:

1). Zoloft drug labels/package inserts;

2).The scientific literature describing the effects of SSRIs, including Zoloft, on serotonin (5-HT) reuptake through its mechanism of action, which includes blocking the serotonin transporter, SERT (5-HTT);

3). The scientific literature regarding the role of 5-HT in cell signaling and embryonic development;

4. My own animal research regarding serotonin signaling and its role in embryonic development (see Lauder et al., '88; Shuey et al., '90; 92; 93; Yavarone et al., 93a,b; Sadler, '11);

5. Published animal and human studies on 5-HT and SSRIs, including Zoloft, as teratogens;

6). Pfizer internal documents;

7). Wilson's principles of teratology;

8) Documents listed on my reference list, attached as Appendix 1.

9) Relevant medical records pertaining to Jessica and M[redacted] G[redacted].

It is a reasonable and standard practice for human embryologists and teratologists to evaluate human epidemiology for evidence of consistency of findings. I considered and evaluated the sources and quality of the publications and science I reviewed as well as the strength, biologic plausibility, and consistency of the information as I do in my work as a human embryologist and teratologist. Upon completion of my review, and analysis of all of the information listed above, I relied on and applied the experience, knowledge, and methodology I have gained and utilized as an embryologist and teratologist studying, teaching, and conducting

research on the origin and prevention of human birth defects at major research universities for over 40 years. Then, after considering the totality of the evidence and employing the methodologies above referenced, I formulated my opinions as stated in the body of this report. My opinions are stated to a reasonable degree of scientific certainty.

There are a number of key terms that are relevant to this report. Zoloft is the trade name for sertraline and it belongs to a class of drugs called serotonin reuptake inhibitors or SSRIs that act as antidepressants. The SSRI class of antidepressants specifically inhibit the reuptake of serotonin. Serotonin is a monoamine that is commonly referred to as neurotransmitters. Serotonin is also important as signaling molecule that regulates cell proliferation, migration, and other processes essential for normal embryonic development. Serotonin is designated as 5-HT and interacts with unique receptors on cells and molecules within cells to produce its signaling effects. Serotonin has a transporter that is important for regulating the intracellular and extracellular concentrations of this molecule. Thus, there is a serotonin transporter, called SERT, that is the target for the SSRIs and is present in the central nervous system and in embryos at nearly all stages of development.

III. Summary of Opinions

Serotonin (5-HT) is an ancient and essential signaling molecule, involved in cell to cell communication in many organisms across all reaches of the animal phyla, from flatworms to fruit flies, to sea urchins, and ultimately all vertebrates and mammals, including man (Lauder, 1993; Azmitia, 2001; Buznikov et al., 2001). As a signaling molecule, 5-HT regulates fundamental developmental phenomena, including cell proliferation, migration, differentiation, and gene expression. In turn, these key processes play essential roles in embryological development in a human fetus. Signaling is regulated by concentrations of 5-HT, and by which 5-HT receptor(s) are activated. There are 7 distinct families and at least 15 subpopulations of 5-HT receptors that are coupled to important signaling pathways. This large number of receptors allows 5-HT to control a diverse array of crucial cellular functions that regulate many aspects of normal embryological development.

Selective serotonin reuptake inhibitors (SSRIs), including Zoloft (sertraline), alter cellular concentration levels of serotonin. As a result, signaling pathways under the influence of 5-HT, that are essential for normal embryonic development, are disrupted thereby causing a

variety of birth defects.

One of the most sensitive stages of embryonic development to the teratogenic effects of SSRIs, like Zoloft, occurs very early, during the second week of gestation, when the embryo is patterned with regard to its left-right (L-R) and anterior-posterior (A-P; head-to-tail) axes. At this early stage, 5-HT is utilized as a signaling molecule to establish the genetic pathway necessary for appropriate L-R patterning. If this signaling is disrupted, as happens with Zoloft and other SSRIs during gestational exposure, then the normal body plan asymmetries that are established by L-R patterning are altered causing laterality defects, also called heterotaxies.

In brief summary, it is my opinion, stated to a reasonable degree of scientific certainty, that ingestion of Zoloft (sertraline) by M[redacted] G[redacted]'s mother, Jessica, during the first trimester of her pregnancy, disrupted serotonin concentrations and cell signaling essential for establishing normal L-R patterning resulting in M[redacted]'s birth defects, including [redacted]. The foundation for my opinions stated herein is based upon my background, training and experience as an embryologist and teratologist, as well as generally accepted scientifically sound evidence, including but not limited to, research, literature and documents regarding SSRIs and Zoloft, known critical roles of 5-HT in cell signaling and a high degree of biological plausibility for the mechanism of injury, as will be set forth more fully in the body of this report.

IV. Teratogens

A teratogen is a chemical, environmental pollutant, pharmaceutical compound, or other toxicant that causes birth defects (Wilson, '77). SSRIs, like Zoloft, are an example of a class of pharmaceutical compounds that act as teratogens, resulting in a variety of birth defects. Like all teratogens, SSRIs, like Zoloft, cause or substantially contribute to birth defects as evidenced by the Principles of Teratology, formulated by one of the pioneers of the science, Dr. James Wilson. Dr. Wilson formulated these principles in 1959 based upon the birth defects disaster caused by the drug thalidomide, which was prescribed to pregnant women as an anti-nauseant. Maternal ingestion of thalidomide caused severe and distinct limb abnormalities in babies exposed to the drug during gestation (McBride, '61; Lenz, '62). The thalidomide tragedy provided a vital lesson because it revealed that drugs could cross the placenta and adversely impact developing fetuses. Dr. Wilson determined that out of thalidomide tragedy, a valuable lesson should be learned: drugs should not be given "indiscriminately" to mothers during pregnancy (Wilson, '77). They can and do cause birth defects, a well-accepted fact in medical and scientific communities today.

According to Wilson's General Principles of Teratology, the teratogenicity of a compound, i.e., the type and severity of the defects it causes, is determined by the following 6 parameters:

1. Teratogenesis, abnormal development due to environmental factors, is a result of the interaction of the genetic identity of the fetus with the environment. Stated another way, Susceptibility to teratogens depends on the genotype of the conceptus and the manner in which these genes interact with the environment.

2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure… and "specific organs can often be rendered abnormal by administering a teratogen during or before the early formative stages of that organ (Wilson, '77)."

3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).

4. The access of adverse environmental influences to developing tissues depends on the nature of the influence (agent). Several factors can affect teratogenesis, such as the duration or amount of exposure to teratogen and the mother's genetic identity.

5. The final manifestations of abnormal development are: Death, Malformation, Growth Retardation, and Functional Defect. "Whatever the differences and interrelations between death, malformation, growth retardation and functional deficit, they can all result from developmental aberrations. There is no logical basis for giving undue emphasis to one over the other in evaluating adverse influences on developmental processes. Traditionally, malformation has been used as the main criterion in estimating adverse effects, probably because structural defects were more conspicuous, but this does not justify ignoring changes in mortality, growth rate, or functional capacity." "Therefore, no estimation of adverse effects on development can be considered complete unless it includes all manifestations of abnormal development. (Wilson, '77)."

6. The manifestations enumerated in the fifth principle increase in frequency and severity as the amount of teratogen in the environment increases from a No Observable Adverse Effect Level (NOAEL) to a 100% Lethal Dose (LD100).

While these 6 principles have stood the test of time, Wilson himself admonished that they were not written in stone and that, "further additions and modifications will be necessary as expansion of the field [teratology] continues, particularly as the little studied subject of mechanisms is explored." Regarding stages of susceptibility to teratogens, he stated," The nature of induction or early chemical determination is still not understood, after more than half a century of study. It is, nevertheless, known to precede structural differentiation by several hours to a few days. Whether differentiation is at the chemical or structural level is largely an academic issue because once groups of cells are destined to have specific roles in organ formation, whether visibly different from other cells or not, such cells probably acquire metabolic individuality. It is assumed that the more specialized the metabolic requirements of differentiated cells, the more liable they are to have specific sensitivities to deprivation or damage." (Wilson, '77).

In Wilson's day, 50-60 years ago, he estimated that the "critical period" of susceptibility to teratogens began near the end of germ layer formation (gastrulation; 18 days after conception). However, based upon modern day techniques capable of characterizing specific times in cell signaling, induction, specification, and differentiation it is clear that "induction and chemical determination" of cells occurs much earlier than Wilson hypothesized, especially regarding specification of the cranio-caudal (anterior-posterior), left- right, and dorso-ventral axes that begin to be established soon after implantation (6-7 days after conception and continue through early gastrulation at days 14-18) (Meyers and Martin, '99; Okada et al.,'05; Fukumoto et al., '05a,b; Tam et al.,'06; Takaoka et al., '07; Rossant and Tam, '09; Takaoka and Hamada, '12;).

In 1972, Dr. Ray Shenefelt, another pioneer in the field of teratology, authored a seminal paper that expounded on Wilson's important principles of teratology by revealing that birth defects can be induced in the same organ or tissue at multiple stages of an embryo's development (Shenefelt, '72: This manuscript was re-printed in 2010 and called a "classical paper in teratology" as a tribute to the significance of this work). The study was conducted using the teratogen retinoic acid with very brief exposure times (so that precise estimates of embryonic stages of development could be ascertained) in order to determine the periods of teratogenic susceptibility ("critical periods") of over 72 organs and tissues. In one example, an analysis of aortic arch and other vascular anomalies, there were multiple periods of susceptibility, including

developmental stages prior to the appearance of blood vessels, when the embryo was in the initial stages of patterning its L-R and A-P axes of development. Indeed, in 25% of the more than 72 malformations that were studied, the "critical period" occurred prior to the appearance of the anlage of that organ (Shenefelt, '72, '10). The fact that organs could pass through multiple stages of sensitivity to teratogens was an important finding, but the fact that their development could be altered so early in the period of embryogenesis was a revelation in the field of teratology.

It should also be noted that a single teratogen or a misexpression of a single gene can produce malformations in multiple organ systems. For example, in addition to altering cardiac development, many teratogens also cause craniofacial malformations because both the heart and the face are dependent upon neural crest cells for normal embryogenesis (Webster et al., '86). Thus, if a teratogen interferes with neural crest cells, both the heart and face can be adversely affected (Webster et al., '86; Sadler, '12). Similarly, disruptions in gene expression that alter signaling pathways can affect more than one embryonic organ or structure as, for instance, mutations in the gene *TBX5,* which is involved in heart and upper limb development, result in cardiac and upper limb defects (heart-hand syndromes)(Fan et al., '03). It is an accepted principle in teratology and embryology that a single teratogen can cause birth defects in multiple organ systems in an exposed fetus. This is not a new or novel concept. The medical and scientific communities acknowledge that a single teratogen can cause multiple organ defects in an exposed fetus, for example retinoid acid and thalidomide, which are noted by the March of Dimes Birth Defect Organization to cause birth defects in multiple organ systems.

Timing for the induction of congenital defects is exquisite, such that a teratogen must be present at the requisite moment in development to have an effect. Thus, if a teratogen operates to alter early endocardial cushion induction and formation during the time when 5-HT uptake occurs in cardiac muscle cells, the teratogen must be present when the myocardium regulates this cushion formation. Further, after this critical period, it is irrelevant whether exposure to the teratogen remains present because a cascade of morphogenesis has been set forth and removal of the teratogen will not reverse the effects. Therefore, it is a fundamental principle of teratology

that each organ system passes through critical periods ("critical moments" as Wilson called them) of development, and the effects of teratogen exposure during these vital developmental stages can and does induce embryological malformations despite subsequent elimination of teratogen exposure, as was so elegantly shown in Shenefelt's study (Wilson, '77; Shenefelt, '72, '10). This scientific evidence is relevant for heart defects because there are 3 time periods during embryonic development when Zoloft's teratogenic effects on 5-HT signaling, induce congenital heart malformations: 1) Days 14-18 when laterality is established and patterning of the primary heart cells occurs; 2) Days 23-28 when lengthening of the outflow tract occurs; 3) Weeks 4-8 when septation of the heart chambers and outflow tract occurs. Optimal concentrations of 5-HT (not too high or too low) are vital for directing each of these morphological events. Thus, based on sound scientific evidence, SSRIs, including Zoloft, can disrupt optimal 5-HT concentrations at critical periods, which can and does induce birth defects, including heart defects.

Susceptibility to teratogens may depend upon the genotype of the mother and/or the embryo. For instance, if the mother has a genetic variation that affects her capacity to metabolize a potential teratogen, the embryo will be exposed to a higher concentration of the toxic compound and for a greater duration. Consequently, there is an attendant increase in teratogenicity and induction of birth defects under such conditions. These types of interactions between the genome and teratogens are called "multi-factorial interactions" (Wilson, '77). Thus, birth defects may be caused solely by genetic abnormalities (15-25%), solely by toxic compounds (10-15%), or, most commonly, by an interaction of the two (multi-factorial causes; 60%). (Czeizel, '05).

Another important factor in determining whether a given drug or environmental factor operates as a teratogen is whether it passes from mother to conceptus/embryo by crossing the placenta. During the critical early stages of organogenesis, the placenta is not yet fully developed. At this stage, the embryo is surrounded by the trophoblast, a shell of cells, which are bathed in maternal blood. The trophoblast, a primitive placenta, appears to take up serum factors from the maternal blood and transport them to the embryo. Diffusion is another method of early maternal-fetal transport of serum factors. Thus, at the vital early stages of embryogenesis, the conceptus can be exposed to potential teratogens including Zoloft, via the trophoblast (Sadler, '12). As an expert in placental differentiation and transport has stated: "….given the multiplicity of available transport systems, when small molecular substances are presented to the

chorioallantoic placenta (via maternal uterine blood flow), the assumption concerning entry into the embryo should be that placental transport occurs…" (DeSesso et al., '12).

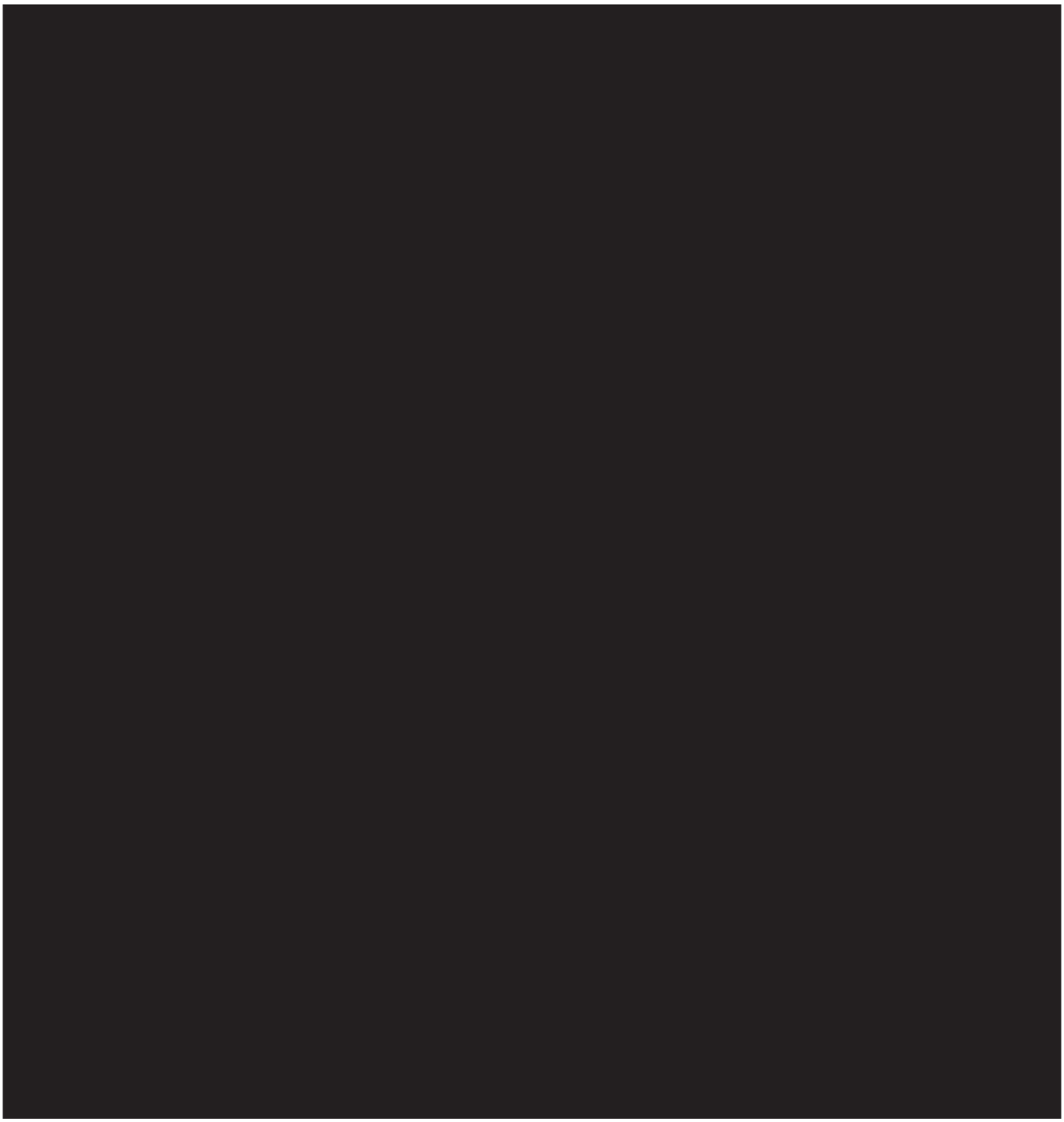
Interestingly, a system of rodent (rat and mouse) embryo culture has been developed that mimics physiological conditions in humans, such that effects of toxins, like Zoloft, alcohol, retinoic acid, and other teratogens, can be studied in controlled conditions (Sadler, '79; Sadler et al., '82; Warner et al., '83; Sadler and Warner, '84). In this system, the rodent visceral yolk sac functions like the trophoblast in human embryos and can be studied to determine if transport of nutrients and other substances, like teratogens, cross the primitive placenta (Warner et al., '83; Jollie, '90). In later stages of development, potential teratogens are passed to the developing embryo via the placenta and SSRIs, including Zoloft, and their metabolites readily cross this organ (Rampono et al., '09). Thus, toxic compounds, like Zoloft, can and do pass from the mother to the conceptus at all stages of embryogenesis.

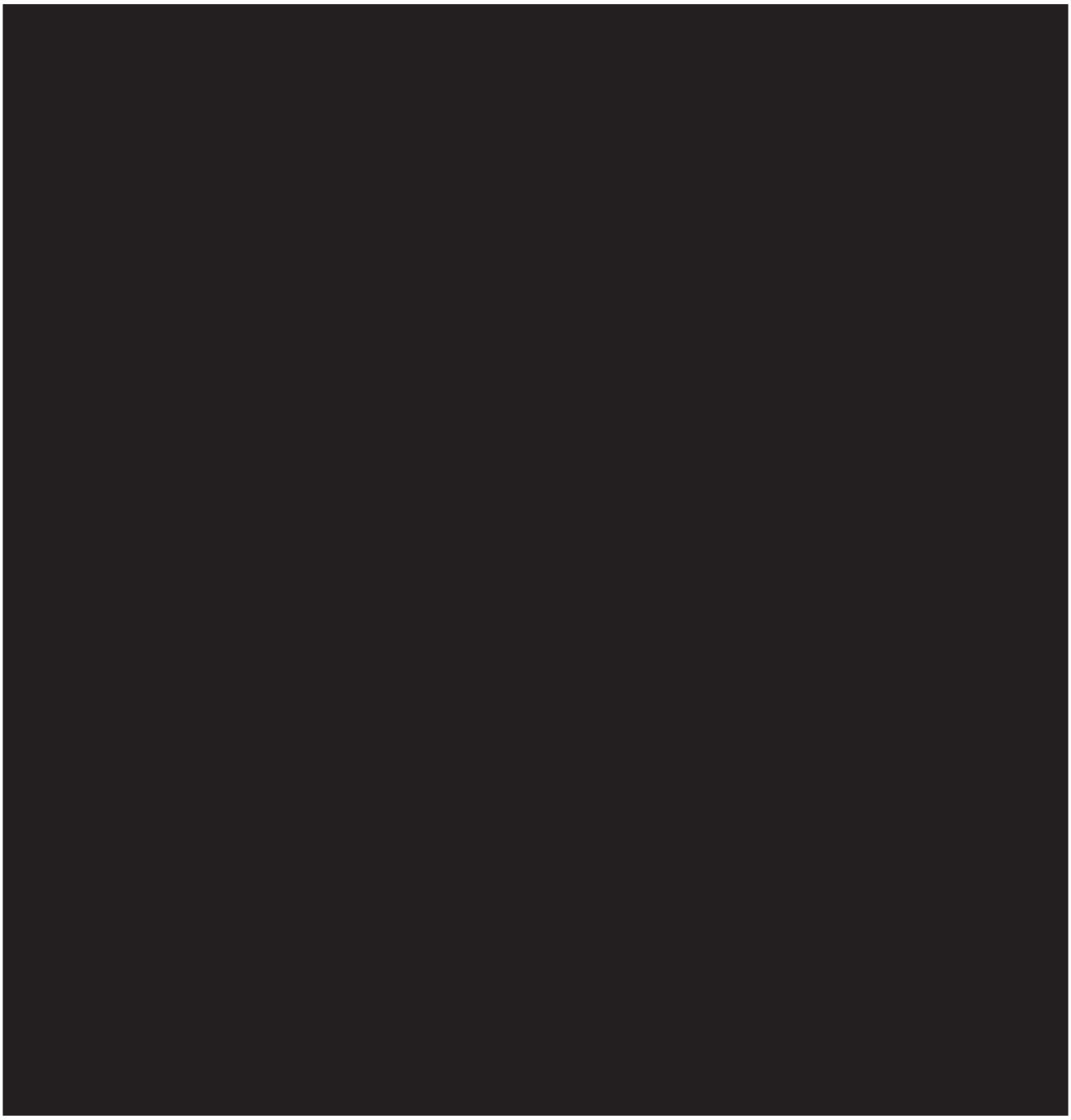
Identification of human teratogens is a multifaceted approach wherein, a number of factors are evaluated. These approaches routinely used by embryologists and teratologists include, but are not limited to, obtaining accurate and thorough maternal histories as well as conducting and evaluating epidemiological and animal studies. Animal studies that employ a variety of species are used to test potential toxins and the data are extrapolated to humans. Extrapolating data from animals to humans is more accurate if the mechanism of action of the teratogen is well-defined and one that is fundamental to normal development for a wide-range of species (Wilson, '77).

For example, 5-HT is a basic signaling molecule vital to normal embryogenesis (see Section V. Signaling Molecules, Buznikov, et al., '64; '70; '72; '81; '84; Lauder, '93; Shuey et al., '90; '92; '93; Yavarone et al., '93: Choi et al., '94a,b; '97; '98; Choi and Maroteaux, '96; Launay et al., '96; Lauder et al., '2000; Fukumoto et al., '05a,b; Adams et al., '06; Blackiston et al., '11; Vandenberg et al., '12; Rea et al., '13). It has been established that by their mechanism of action of blocking the serotonin transporter, SERT, SSRIs, including Zoloft, alter extracellular 5-HT concentrations (Fox et al., '07), which in turn disrupts cell signaling that is essential for establishment of Left-Right asymmetry, proper patterning of heart progenitor cells, and for normal neural crest cell development in embryos. Furthermore, these embryonic phenomena and 5-HT's role in regulating them are fundamental processes that occur in all vertebrate species, humans and animals, and which are processes essential for normal heart development.

Therefore, assessment of the above-referenced factors facilitates accurate determination as to whether drugs, like SSRIs, including Zoloft are teratogenic.

The probability of the determination of a drug's teratogenicity is further strengthened when evidence from animal studies documents the "final manifestations of abnormal development," including "death, growth retardation and malformations" (Wilson, '77).





Before a drug company can market a drug for use by people, they are required to do testing on animals to see if they are safe to use in humans. This approach is standard practice and is done because of the usefulness of evaluating potential risk or safety issues in humans. As stated in the Reference Manual on Scientific Evidence (2d ed Fed. Jud. Center 2000. D. *Extrapolation from Animal and Cell Research to Humans*), results from testing in animals can be expected to be seen in humans. Considering the developmentally toxic effects of Zoloft revealed

in the preclinical animal studies, together with the fact that 5-HT is an important molecule for regulating fundamental processes of embryogenesis in both humans and animals, and the fact that the mechanism of action of the SSRIs, including Zoloft, is to alter 5-HT's concentrations in the extracellular space, thereby disrupting cell to cell signaling (Fox et al., '07), it is scientifically logical to conclude that a well-defined mechanism of injury exists. Thus it is scientifically reasonable to extrapolate the data from animal studies to human experience with greater confidence, and to reach the sound conclusion, to a scientific degree of probability, that SSRIs, including Zoloft, are teratogenic. This opinion is buttressed by the fact that numerous peer-reviewed epidemiology studies have demonstrated an association between in utero exposure to Zoloft during the first trimester of pregnancy and birth defects.

It is a reasonable and standard practice for human embryologists and teratologists to evaluate human epidemiology for evidence of consistency of findings and I have done so, as I do in my work as a human embryologist and teratologist, and conclude the human epidemiology is consistent with the in vitro and animal research findings of teratogenicity with these compounds. For example, as a class with the same mechanism of action, SSRIs have been shown to increase the incidence of birth defects (Wogelius, '06; Kornum, '10; Malm, '11; Jiminez-Solem, '12). Also, as a class effect they have been shown to cause heart defects (Alwan et al., '07; Bar-Oz, '07; Louik et al., '07; Merlob, '09; Pedersen, '09; Kornum, '10; Colvin, '11; Malm, '11; Jiminez-Solem, '12).

Zoloft itself has been associated in multiple peer-reviewed studies with an increased risk of heart malformations. Zoloft was associated with a statistically significant doubling of the risk of septal defects in Louik et al, published in the New England Journal of Medicine in2007 with an adjusted OR 2.0 (95% CI 1.2-4.0); with a statistically significant tripling of the risk of septal defects in Pedersen, et al, published in the British Medical Journal in 2009 with an adjusted OR 3.25 (95% CI 1.21-8.75); with a statistically significant tripling of the risk of cardiac malformations (adjusted OR 3.0 (95% CI 1.4-6.4) and septal defects (adjusted OR 3.3 (95% CI 1.5-7.5) in Kornum, et al, published in Clinical Epidemiology in 2010); with a statistically significant tripling of the risk of VSDs (adjusted OR 3.60 (1.86-6.96)), and a statistically significant over doubling of the risk of congenital malformations of the heart (adjusted OR 2.73 (1.75-4.26) in Jiminez et al, published in the British Medical Journal in 2012; and with a statistically significant increase in Atrial and ventricular septal defects (RR 1.34 (1.02-1.76),

Berard et al published in the American Journal of Obstetrics and Gynecology in 2015. Thus there is replicated, statistically significant human epidemiology demonstrating that Zoloft increases the risk of congenital heart malformations in humans exposed in the first trimester. Of particular interest is the fact that, in addition to heart abnormalities, malformations that are often observed in individuals with laterality defects (who have abnormalities of their Left-Right axis), including omphalocele and anal atresia, have been linked to the use of Zoloft (Louik et al., '07). Furthermore, as a class, these drugs have been associated with an increased incidence of omphalocele (Alwan et al, '07) and with vascular defects, which are hallmarks of adverse effects on laterality signaling (Kosaki and Casey, '98; Colvin et al, '11).

Despite these findings, many birth defects caused by SSRIs, like Zoloft, may have gone undetected because babies with severe birth defects are often spontaneously aborted or electively terminated and, thus, omitted from the data. As illustrative of this point, the risk of spontaneous or elective abortion is low for a baby with cleft lip, and virtually all of these babies would be born and counted. On the other hand, a significant number of babies with severe heart or other major defects may be spontaneously aborted or the defect may be diagnosed in utero and the pregnancy electively terminated. Consequently, collection of epidemiological data concerning severe heart and other defects from live born infants will fail to detect the true account of the incidence of heart or major malformations produced by a teratogen.

A similar problem can arise in animal studies where embryos and fetuses with severe defects may be spontaneously aborted (resorbed) and, thereby, omitted in the data representing the incidence of congenital defects. Typically, abortion (resorption) sites can be counted and recorded. However, birth defects responsible for the occurrence of the abortion cannot usually be determined because of tissue deterioration. Also, there may be extensive post-natal death of animal offspring where they have severe congenital malformations. In such a case, detailed necropsies are essential to determine the causes for these deaths, and to accurately identify the birth defects that may have been contributing factors. Therefore, animal and human epidemiological data may under-represent the true association between a given teratogen and congenital birth defects. The fact that SSRIs, like Zoloft, have been associated with an increase in spontaneous abortions (Hemels, et al., '05; Diav-Citrin, '08; Yonkers, '09; Broy et al,, '10; Domar et al, '13), that Pfizer's own preclinical animal studies showed an increase in stillborns, and the fact the Prozac, another SSRI, also caused an increase in resorptions (spontaneous

abortion) in mice (Bauer, 10) indicates that many babies potentially having birth defects, including those with heart defects, have been lost to follow up due to prenatal death or loss of the embryo or fetus and consequently the numbers of birth defects produced by these drugs is under-estimated.

One difficulty in identifying human teratogens relates to the nature of birth defects and their occurrence rate. Overall, birth defects occur at a rate of approximately 3% of live born babies. Within the realm of birth defects, a "common" birth defect is one that arises with an occurrence rate of 1 per 1000 births, for example, neural tube defects. Heart defects occur in approximately 1 per 100 births. Typically, teratogens do not cause dramatic increases in occurrence rates, and as such, it can be difficult to identify whether a new drug or environmental compound as a teratogen. For example, as noted previously, an increased risk of at least twofold for heart defects is associated with maternal use of Zoloft. This doubling of risk means that instead of 1 baby in 100 being born with a heart defect there will be 2. So, in 1000 births, there will be 20 instead of 10; in 10,000 births there will be 200 instead of 100 and in 100,000 births there will be 2000 instead of 1000. A thousand more babies with heart defects is a significant number, poses a significant cost both emotionally and economically to families with the children, and represents a significant health care burden for the state, especially since heart defects did not have to occur in these babies at all. Since it has been estimated that as many as 13.4% of pregnant women are using antidepressants (Cooper et al., '07), the total number of affected babies with heart defects is quite high. And heart defects are only one of several malformations for which epidemiological studies have shown an increased relative risk in women using Zoloft.

In summary, identification of human teratogens is not a new or novel process, but rather, employs a well-proven multifaceted and scientific approach that utilizes evaluation of a number of factors, as referenced above. In coming to my opinions in this case, I have employed and evaluated the facts and totality of the evidence under these referenced scientific methods which are consistent with the scientific methodology I was taught during my education and training and work with colleagues over several decades, have taught students and healthcare providers and which I have utilized as a human embryologist and teratologist for over 40 years.

V. Mechanisms of action of SSRIs and Zoloft

Wilson was particularly keen on understanding mechanisms of teratogenesis (Principle 3)…"mechanisms are thought to occupy a pivotal position in the series of events between the causative factor in the environment and the ultimate expression of developmental abnormality, the final defect. They represent the earliest identifiable reaction of the developing system to the environmental cause. They usually are at the subcellular or molecular level, hence are not readily apparent by ordinary means (Wilson, '77)." Thus, because of their nature and the limited cellular and molecular scientific approaches available in Wilson's day, the understanding of mechanisms was restricted. However, these limitations did not prevent Wilson from grasping the significance of determining and understanding mechanisms of teratogenesis. As he stated, "It is clear from the [aforementioned] that information on teratogenic mechanisms is limited, but it may not be apparent why a knowledge of mechanisms is important. Pragmatists have argued that a machinist is able to repair an engine without understanding the theory behind its operation. But teratology is concerned with more than repair. One of the major objectives is to anticipate risks before they materialize. The anticipation of teratic risks in today's rapidly changing environment becomes an endless succession of screening tests unless a knowledge of mechanisms can lead to extrapolations, generalizations, and shortcuts that will simplify the task. Furthermore, the use of animal tests for evaluation of human risk will become more than empirical only when the degree of comparability of mechanisms between test animal and man is understood. Finally, with a better understanding of mechanisms, unknown causes may be more easily recognized (Wilson, '77)." Thus, a knowledge of mechanisms is essential to predicting and preventing birth defects.

The United States FDA assigns chemical compounds to an established pharmacologic class when it enters the United States market. Based on the common mechanisms of teratogenicity for the class of SSRIs, it is scientifically reasonable to evaluate and rely upon data for the class of SSRIs when looking to the effects of a specific SSRI, such as Zoloft. Regardless of their chemical structure, the SSRIs, like Zoloft, meet the FDA's requirements for acting as a class of compounds. These requirements include: 1) Mechanism of action at the receptor, membrane, or tissue level; 2) Pharmacological effect at the organ, system, or whole body level; 3) Chemical structure. Drugs are considered a pharmacological class if they meet any one of the three criteria (FDA Guidelines for Industry and Review Labeling for Human Prescription Drug

and Biological Products- Determining Established Pharmacological Class for Use in the Highlights of Prescribing Information, October 2009 Labeling). Clearly, the SSRIs meet the first two criteria and, therefore, represent a class of compounds. They also meet the standard proposed by Wilson for a class of compounds with predictable mechanisms of action, here shared by each of the drugs in the class of SSRIs.

Likewise, a large body of epidemiological literature evaluates human fetal risk by evaluating SSRIs as a group based on their common mechanism of action. For example, Tuccori concludes that SSRIs are a class and that they cause malformations (Tuccori et al., '10). Jiminez-Solem shows that SSRIs increase the incidence of malformations as a class (Jiminez-Solem et al., '12) and Colvin concludes that as an aggregate SSRIs cause birth defects (Colvin et al., '11). In another study, Pedersen concludes, "Our results suggest a class effect of the SSRI on heart defects…" (Pedersen et al., '09). Furthermore, animal studies using mice that are lacking the serotonin transporter SERT (5-HTT), which is normally blocked by SSRIs to increase extracellular concentrations of 5-HT and to produce their antidepressant effects, do not respond to these drugs, which again shows a class effect for these compounds (Fox, et al., '07). [redacted] Also, in peer reviewed publications, their scientists have stated that, "sertraline belongs to the class of selective serotonin uptake inhibitors (SSRIs)" (Davies and Klowe). Thus, employing the same methodology utilized by Pfizer and by numerous researchers and epidemiologists who have conducted peer-reviewed epidemiologist studies, I concur that the SSRIs are a class and they have the same mechanism of action and have considered this in conducting my analysis and forming my opinions.

Thus, based on the SSRI's common mechanism of action, vis a vis, blocking serotonin reuptake, the SSRIs are a class of compounds. Furthermore, it is that same mechanism of action that causes them to be teratogenic. Based on the fact that this mechanism of action was known since the creation of SSRIs; that 5-HT reuptake in embryos is a key event in regulating effective signaling concentrations essential to normal embryogenesis; that epidemiology studies

demonstrate that birth defects are associated with these drugs; and that Wilson indicated that knowing the mechanism of action of a drug was paramount to extrapolating its potential teratogenic effects to humans, Pfizer should have appreciated and anticipated the teratogenicity of Zoloft. Regarding their ability to cause birth defects, it is the SSRI's mechanism of action that is the single most important determinant of their class effect. All of these drugs are designed to block 5-HT uptake by the 5-HT transporter SERT, thereby increasing extracellular 5-HT concentrations at the synapse between two neurons and in the extracellular space between embryonic cells (Fox et al., '07). These altered concentrations in embryos disrupt normal signaling pathways through which 5-HT regulates cellular events essential to normal embryogenesis (see Section VI, Signaling Molecules).

A second mechanism whereby SSRIs can disrupt embryonic cell to cell signaling is by adversely affecting the membrane potential (Vmem) between the inside and outside of cells by either blocking SERT, and disrupting 5-HT concentrations, or by binding directly to ion channels important for maintaining Vmem and disrupting their function. Vmem in cells is regulated by ion channels and proton pumps and the spatio-temporal patterns of Vmem within and among tissues during embryogenesis create a network of bioelectric signals that regulate gene expression. For example, the genes *Slug, Snail,* and *Sox 10* are involved in directing cells to assume a migratory phenotype and are regulated by Vmem (Morokuma, et al., '08; Blackiston et al., '11). Furthermore, Vmem changes are involved in regulating transcription, cell shape, migration, and differentiation that are essential processes for normal development (Forrester et al., '07; Levin and Stevenson, '12; McCaig et al., '09; Tseng and Levin, '12; 13). Vmem in developing cells also regulates patterning of organs and tissues, as in the case of establishing Left-Right asymmetry, a critical factor in normal heart and vascular development (see Section V. Establishment of the Body Axes and Patterning in the Early Staged Embryo: Increased Sensitivity to SSRI (Zoloft)-induced Teratogenesis. (Altzer et al., '01; Borgens, '84; Jaffe and Vanable, '84; Levin, '07b; 12a; McCaig et al., '02; '05; '09; Nuccitelli, '03). This process is disrupted when Vmem is altered by the ability of SSRIs to interact directly with ion channels and to modify their function (Aldana and Stiges, '12; Chien et al., '11; Feurbach et al., '05; Fonseca-Magalhaes et al., '11; Fryer and Lukas, '99; Huang, 06; Kalyoncu, '99; Kabayashi et al., '11; Maertens et al., '02; Wang et al., '08b; Witchel et al., '02; Ohno et al., '07; Wang et al., '08b).

VI. Signaling Molecules

Another axiom of teratology, illustrated by Shenefelt's seminal study, is that the same teratogen can produce a variety of birth defects. This concept applies to SSRIs, including Zoloft. Dr. Shenefelt's study employed the teratogen retinoic acid which was shown to alter many cellular events, including cell death (apoptosis), cell proliferation, extracellular matrix production, and others that can result in birth defects (Shenefelt, '72, '10). Importantly, another phenomenon disrupted by retinoic acid is cell signaling. As our knowledge of genes and molecular biology increases, it is becoming abundantly clear just how important cell signaling and signaling pathways are to normal development. Cells communicate with each other using signaling molecules that interact with receptors, thereby initiating signaling pathways (*Langman's Medical Embryology,* Chapter 1, 13th Ed.). In this way, signaling molecules instruct cells to produce certain organs or tissues. For example, signaling molecules called Fibroblast Growth Factors (FGFs) regulate lengthening of the limbs. Another signaling pathway, involving Sonic Hedgehog (SHH), ensures that the thumb and little finger are correctly positioned (Adapted from *Langman's Medical Embryology*, 12th ed.; Benazet and Zeller, '09). Teratogens, including Zoloft, can perturb normal signaling and disrupt these pathways, which results in a variety of birth defects, depending on the time in development when signaling is altered, and the signaling molecule or its receptor that is targeted.

Interestingly, the same signaling molecule is often employed in the development of multiple tissues and organs. For example, SHH is involved in brain, vertebral, limb, and craniofacial development (Varjosalo and Taiple, '09). Similarly, members of the same family of molecules, such as FGFs, BMPs, TGFβs, WNTs and others are employed in formation of multiple embryonic structures from limbs to the central nervous system. Thus, a single molecule or family of molecules can regulate development of multiple embryonic organs and tissues. In part, receptors for these molecules make this possible. Typically, there are multiple receptors for each signaling molecule, such that the same signal can be interpreted by different cell types, depending upon the receptors that the given cells possess. It is as if a signal molecule contains different codes and how a cell responds depends on which codes can be read by which receptors located on different cells, such that some form limbs, others palate, etc. 5-HT is a critical signaling molecule that is employed in the formation of multiple organs and tissues (Lauder, '93; Azmitia, '01; Buznikov et al., '01). In addition, 5-HT plays a crucial role in establishing the L-R

axis and patterning of cells at the earliest stages of embryogenesis (Yost, '98; Fukumoto et al., '05a,b; Levin, '05; Levin et al., 06; Vandenberg et al., '13). To regulate these different events, 5-HT utilizes seven families of receptors and fifteen subtypes of these receptors within the families which allows 5-HT to signal multiple events that regulate key developmental processes, such as gene expression, cell proliferation, differentiation, and migration (Azmitia, '01; Kroeze et al., '02).These signaling pathways explain how SSRIs and Zoloft cause a variety of birth defects. As with any signaling molecule, there is an optimum concentration that is required for activation of receptors, such that too much or too little of the signal molecule, in this case 5-HT, disrupts the pathway and triggers abnormal development. Because SSRIs including Zoloft block reuptake of 5-HT at SERT sites, they alter 5-HT intracellular processes that would be initiated by the blocked serotonin as well as altering extracellular concentrations, either of which result in disruption of 5-HT signaling essential to normal embryogenesis.

The type of birth defect produced by Zoloft is determined by the well-established and widely accepted principles of teratology, as determined by Wilson ('77) and Shenefelt ('72, '10). Based upon these principles, one can reasonably state that if a woman ingests Zoloft, early in her pregnancy when cells are being patterned (2^{nd}-3^{rd} weeks), multiple and different types of birth defects can be produced. If the drug is taken later in gestation (3^{rd} to 8^{th} weeks), the type of birth defect caused will be determined by the drug's effects on whichever developing organ system is vulnerable at the time. Of note, however, is that early disruption of cell signaling has a downstream effect such that early exposure can alter cell signaling subsequent to that exposure and result in malformations. The outcome will also be influenced by dose of the teratogen, duration of exposure, and the other principles of teratology as set forth above by Wilson ('77) and Shenefelt ('72,'10).

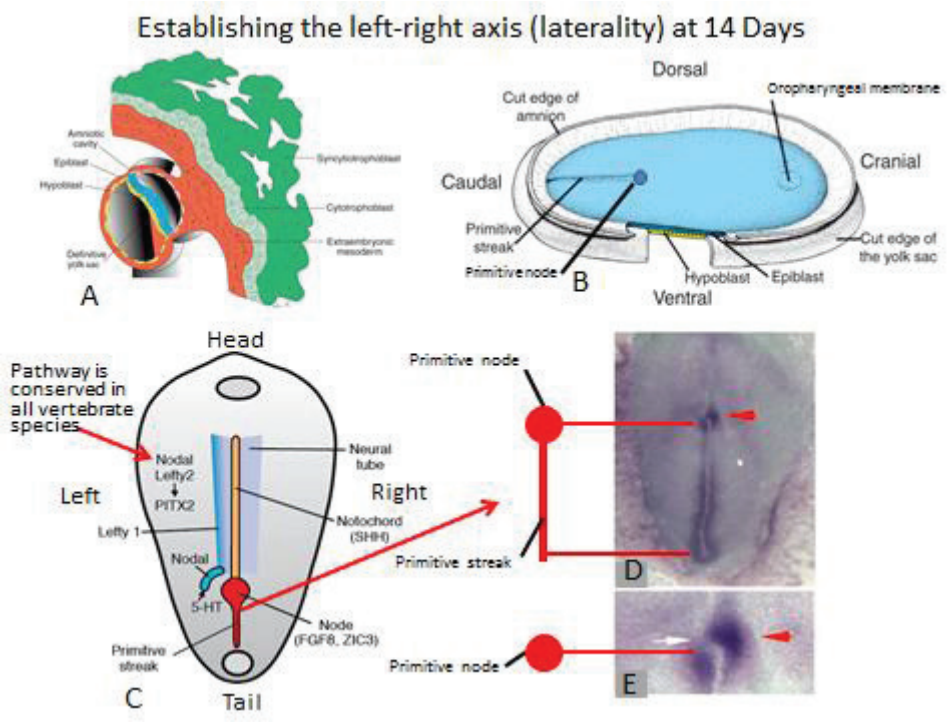
VII. Establishment of the Body Axes and Patterning in the Early Staged Embryo: Increased Sensitivity to SSRI (Zoloft)-Induced Teratogenesis

Establishment of the body axes is a critical time during very early development when the Anterior-Posterior (A-P; Cranio-Caudal), Dorso-Ventral (D-V), and Left-Right (L-F) axes in an embryo are specified. This specification is essential to normal embryogenesis because development of all the organ systems will be directed and controlled by this plan. The process is similar to building the framework of a house: If one side is taller than another, or too long, or off

center, then the rest of the house cannot be built without defects. The roof will not fit, or a door will not close, or the plumbing will be impossible to position properly. So it is with embryos: If the axes are not specified correctly then defects occur. Many of the defects that arise are due to abnormal specification of the L-R axis and are called laterality defects or heterotaxy (Ramsdell, '05). These defects may occur in the midline or on the left or right side, they may be represented by abnormal placement of body organs, and they may involve one or multiple organs (Martinez-Frias, '95; Martinez-Frias et al., '95; Gebbia et al., '97; Kosaki and Casey, '98; Ticho et al., '00; Morelli et al., '01; Bisgrove et al., '03; et al., '04). By far the most sensitive organ to abnormal L-R axis formation is the heart, probably because it has such distinct left and right sides and the fact that it is normally re-positioned from the midline to the left side (Kathiriya and Srivastava, '00).

The first axes to form are the A-P and D-V axes and they begin to be specified in the peri-implantation period soon after the blastocyst forms, about days 5-6 of development (Takaoka et al., '07; Rossant and Tam, '09; Takaoka and Hamada, '12). By the time of implantation, the A-P axis is firmly established (days 6-7; Takaoka and Hamada, '12). When establishment of the L-R axis begins is not entirely clear. There is evidence that L-R asymmetry begins when the dorsal-ventral axis is specified, which would be near the time of implantation at 5.5-6 days (Yost, '98; Takaoka et al., '12). In any case, laterality is clearly being regulated when the primitive streak and node form on approximately days 14-16 (Meyers and Martin, '99; Okada et al., '05;Tam et al., '06; Fukumoto et al., '05a,b). At this stage, the embryo is in the form of a bilaminar disc, like an oreo cookie without the icing (Fig. 1A and B). The anlage of organ systems are not yet present. One of the signaling molecules essential to establishing the L-R axis of the embryo is 5-HT (Fukumoto et al., '05a,b;Vandenberg et al., '13). At this point in embryogenesis, increased concentrations of 5-HT on the left side side, signal through a transcription factor *MAD3* to restrict expression of *NODAL*, another signaling molecule, to the left side, (Fukumoto et al., '05a,b; Levin, '05; Levin et al., '06; Vandenberg et al., '13). The serotonin transporter SERT, the target for SSRIs like Zoloft, also plays an essential role in this process by maintaining appropriate concentrations of serotonin in the region of the primitive streak and node so that signaling can occur (Fig. 1D and E; Fukumoto et al., '05a,b). This differential localization of these 2 molecules, which also occurs in mammals (Figs. 1E and F), triggers a signaling pathway ending with expression of *PITX2*, essentially, a master gene for left

sided development (Fig. 1; Bisgrove et al., 03; Ramsdell, '05). This *NODAL* to *PITX2* pathway is present in all vertebrate species (Kathiriya and Srivastava, '00; Bamforth et al., '04) and the differential localization of serotonin and SERT and its importance for laterality signaling has been documented in frogs, chicks, and mammals (rabbits; Fukumoto et al., '05a,b; Levin report to Sadler, '15). Patterning of the A-P axis is also continuing and the midline is established, in part, by expression of *SHH* (Bisgrove et al., '03; Aw and Levin, '09). During this patterning process, it is essential that both pathways, L-R and A-P (Fig. 1), interact (communicate) to coordinate development of both axes so that organs are placed in the proper position within the body and midline structures, like the neural tube and ventral body wall, develop normally (Bisgrove, et al., '03; Levin, '05; Takaoka et al., '07; Aw and Levin, '09).



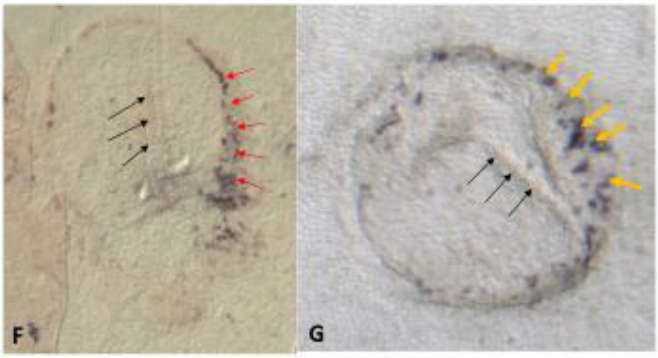


Figure 1. Establishing the left-right (L-R) axis. **A.** Drawing showing a cross section through an implantation site at 14 days after conception. The embryo consists of 2 layers: the epiblast (blue) dorsally and the hypoblast (yellow) ventrally and has a slightly elongated shape. It is positioned between the yolk sac ventrally and and amniotic cavity dorsally in a manner similar to a chick embryo. **B.** Dorsal view of an embryo at a stage similar to the one in **A** that has been removed from its implantation site. A groove, called the primitive streak, with a round depression at its cranial end, called the primitive node, is formed at the caudal end of the embryo in preparation for formation of the germ layers by gastrulation. By this stage, the anterior-posterior (A-P; cranio-caudal) axis is well established. **C.** Drawing showing the same 14 day stage of development to illustrate the signaling molecules and pathways that establish laterality, pathways that are conserved in all vertebrate species. Serotonin (5-HT) is concentrated on the left side of the node and restricts *nodal* expression to this side. This distribution of nodal initiates a signaling pathway in the lateral plate mesoderm involving *Lefty2* and other genes that culminates in expression of the transcription factor *PITX2* that is the master gene for establishing the left side of the embryo. Other genes in the midline assist in restricting this signaling pathway to the left side and coordinate formation of the A-P and L-R axes. Signals regulating development of the right side remain a mystery. **D and E.** Photographs of the primitive streak and node regions in a chick embryo stained to demonstrate localization of the 5-HT transporter SERT. Note that SERT is asymmetrically concentrated in the region of the node where signaling by 5-HT is occurring. The role of the SERT protein is to regulate 5-HT concentrations for normal signaling and it is this molecule that is the target of SSRIs, like Zoloft. **E.** Photograph of a rabbit embryo at the primitive streak stage (Black arrows indicate the location of the streak) showing the asymmetric localization of 5-HT (Red arrows). **F.** Photograph of a rabbit embryo at the primitive streak stage (Black arrows indicate the location of the streak) showing the asymmetric localization of the serotonin transporter SERT (Yellow arrows).

Because 5-HT is an important signaling molecule for establishing the L-R axis in embryos, maternal ingestion of SSRIs including Zoloft at this critical early stage of embryogenesis, can disrupt L-R signaling by altering extracellular 5-HT concentrations and

interfering with 5-HT entering cells through SERT sites and initiating key intracellular processes. Such a disruption can result in "laterality" defects in the developing embryo/fetus (Fukumoto et al., '05a,b).

Normally, many body organs exhibit asymmetry, including the heart, blood vessels, lungs, gut tube, spleen, stomach, liver, and gall bladder. Normal positioning of thoracic and abdominal organs is called *situs solitus*. Complete reversal of all organs, where organs are reversed in a mirror image arrangement, is called *situs inversus*. Discordant organ positioning with respect to symmetry, where one or more organs are abnormally positioned (i.e. reversed in position) or if isomerisms or inversions are present, is called *situs ambiguus* or heterotaxy. These individuals are considered to have "laterality" defects (Ramsdell,'05) and these defects arise because of a failure to correctly establish left-right patterning during embryogenesis.

Individuals with situs inversus do not have a high risk for having other congenital abnormalities, although they do have an increased risk for congenital heart defects (Ferenz et al., '85; Nugent, 94) and their progeny are at an increased risk of having laterality disease with a greatly increased risk for complex cardiac malformations (Burn, '91; Gebbia et al., 97; Casey, '98). However, individuals with heterotaxy often have other congenital abnormalities, including a variety of midline malformations (Martinez-Frias, '95; Gebbia et al., '97; Kosaki and Casey, '98; Ticho et al., '00; Morelli et al., '01; Bisgrove et al., '03; et al., '04). Furthermore, 90% of these individuals will have complex congenital heart defects (Nugent, '94) and many will have abnormal vascular patterns involving the major vessels. (Colvin et al., '11; van Mierop et al. ;Ware et al., '04). Interestingly, within a cohort of individuals with known abnormalities in their laterality signaling pathway, some will have overt heterotaxy or anomalies of organ position, while others will have isolated defects, especially heart malformations, but also midline abnormalities, such as neural tube defects, anal atresia, and omphalocele (Morelli et al., '01; Bisgrove et al., '03; Ware et al., '04).

The most sensitive organ to be affected by abnormal L-R patterning is the heart. Virtually every type of heart defect can be observed where there is perturbation in L-R patterning signals, even in the absence of defects to other organs (Kathiriya and Srivastava, '00; Ramsdell, '05). Thus, atrial septal defects (ASDs), ventricular septal defects (VSDs), l and d transpositions of the great arteries (TGAs), double outlet right ventricle (DORV), dextrocardia, ventricular inversions and isomerisms, atrial inversions and isomerisms, hypoplasia of either ventricle, mitral and

tricuspid atresias, abnormal positioning of the atrioventricular valves, and many other congenital cardiac defects result from abnormal signaling in the laterality pathway (Dagle et al., '93; Kathiriya and Srivastava, '00; Gormley and Nascone-Yoder, '03; Bamforth et al., '04; Ramsdell, '05; Ramsdell et al., '06, Sadler, '11), as can occur when concentrations of 5-HT are altered by SSRIs like Zoloft (Fukumoto et al., '05a,b; Table 1). Because most of the vasculature in an embryo begins as a bilaterally symmetrical system that then is re-patterned into the final form, vascular abnormalities, such as aortic arch defects and vena cava defects, as well as total and partial anomalous pulmonary venous return (TAPVR and PAPVR), commonly arise when abnormal laterality signaling occurs (Van Mierop et al., '72; Rose et al., '75; Heinemann et al., 94; Kosaki and Casey, '98; Morelli et al., 01; Ware et al., '04). In fact abnormalities of the pulmonary vessels, like TAPVR and PAPVR, are almost pathognomonic for laterality defects and occur in over 70-80% of cases (Van Mierop et al., '72; Ware et al., '04). The types of heart and vascular defects are so varied because the heart and blood vessels are dependent upon critical L-R and A-P signaling to acquire their normal development and positioning (Kitamura et al., '99; Liu et al., '02; Bisgrove et al., '03; Ramsdell, '05). Perturbation of this signaling at the earliest stages of embryogenesis, as caused by prenatal exposure to SSRIs, like Zoloft, can and does induce a number of complex cardiac and vascular malformations, which are considered manifestations of abnormal laterality signaling (Kosaki and Casey, '98).

The link between establishing laterality and the occurrence of heart defects has also been documented in animal studies since at least the mid 1990's. For example, in a study that exposed rat embryos to X-irradiation at primitive streak stages prior to organ formation (day 9 in rats; days 14-16 in humans), defects in laterality were observed that included complete situs inversus, but also heterotaxy where not all of normal body asymmetry was reversed. Some of these animals with laterality defects also had malformations of the brain, eyes, spinal cord, face (clefts), heart, aortic arches, vertebrae and kidneys, whereas other embryos had one or more of these malformations, but with normal situs (Wilson et al., '53). A similar study using trypan blue as a teratogen, also administered at the primitive streak stage, resulted in laterality defects characterized by complete and partial situs inversus as well as heart, aortic arch, neural tube (anencephaly; spina bifida) and eye malformations (Monie et al., '66). Heart defects observed in these studies included, dextrocardia, transposition of the great arteries (TGAs), ventricular inversions, absent mitral and tricuspid valves, double outlet right ventricle (DORV), ventricular

septal defects (VSDs), atrial septal defects (ASDs), tricuspid and mitral stenosis, common truncus, common atrioventricular canal, and total anomalous pulmonary venous return (TAPVR); in summary virtually every type of heart defect.

These studies demonstrate that the primitive streak stage is a "critical moment" for establishing laterality and for the induction of heart defects. That this stage is critical for establishing laterality was also illustrated by studies in chick embryos that were treated with the SSRI fluoxetine (Prozac) at the primitive streak stage. Results showed that expression of key genes involved with laterality signaling, that were downstream from a signal from serotonin (5-HT), was disrupted and that this disruption caused laterality defects in the exposed embryos (Levin et al., '95; Fukumoto et al., '05a).

This association between abnormal laterality patterning and isolated heart defects has been proven in studies of family members with known mutations to laterality genes. In such families, a high incidence of family members exhibit only a congenital cardiac defect and no other abnormality (Casey and Hackett, '00; Morelli et al., '01; Bisgrove et al., '03; Ware et al., 04). Based on these data, one of the criteria for diagnosing problems with laterality signaling and establishing the L-R axis is for a patient to have a heart malformation and have family members with heterotaxy (Morelli et al., '01; Bisgrove et al., '03). It is also probable that many individuals with cardiac defects also have other abnormalities associated with disrupted laterality signaling, but these alterations go undetected because they do not cause any clinical symptoms. In fact, the lack of clinical symptoms is a main reason why laterality defects go under-reported in the general population. Therefore, when 5-HT signaling is disrupted during embryogenesis, as results from SSRI ingestion, including Zoloft, such that L-R patterning is perturbed, offspring may exhibit isolated heart defects and/or vascular abnormalities (particularly involving the pulmonary vessels). The reason the heart is so sensitive to abnormal laterality signaling is because it has more laterality than most other organs with its 4 different chambers and vessel patterns and because this laterality is patterned during the formation of the earliest heart cells during gastrulation (approximately days 14-18). Like the analogy with the frame of a house, if one part of the frame or if one part of axis specification is incorrect, many different types of problems can arise in the finished product, depending on where and when the framing/axis defect occurred.

Abnormal laterality patterning would also be expected to result in increased pregnancy loss. A tenet of Wilson's principles of teratology holds that the earlier in gestation that an embryo is exposed to a toxic agent the more likely that embryo is to be severely affected and spontaneously aborted (Wilson,'77). Since patterning of the embryonic axes is so important to normal development, and because it occurs so early in gestation, disruptions of this process would be expected to cause severe abnormalities, which in many cases, would result in spontaneous abortion. Such an increase in this type of pregnancy loss has been shown to occur in women taking SSRIs like Zoloft during pregnancy (Yonkers, '09; Baur et al., '10; Broy and Berard, '10)

VIII. Heart Development and SSRI (Zoloft)-induced Malformations

As stated under section IV above, which describes the importance of laterality to the origin of many of the birth defects observed in offspring of women taking SSRIs, including Zoloft, virtually every type of cardiac defect can occur if 5-HT signaling is disrupted during the establishment of L-R symmetry. When this establishment begins is not entirely clear. It has been suggested that L-R asymmetry occurs when the dorsal-ventral axis is specified, which would be near the time of implantation at 5.5-6 days (Yost, '98; Takaoka et al., '12). In any case, by 14 days the process is definitely occurring as evidenced by animal experiments demonstrating that heterotaxy and multiple other defects result from teratogenic exposures at that stage (Wilson et al., '53; Monie et al., '66) and by experiments showing that disruption of key laterality signaling events with SSRIs causes mis-expression of these important signals and laterality defects (Levin et al., '95; Fukumoto et al., '05a). At this stage the embryo appears as a bi-laminar disc, like an oreo cookie without the icing. The top layer is the epiblast and it has a shallow groove, the primitive streak, in its surface at the caudal end of the embryo; the bottom layer is the hypoblast (Fig. 2A). All of the cells for the embryo are derived from the epiblast by the process of gastrulation, whereby some cells from the epiblast migrate towards the primitive streak and a round depression at its cranial end called the primitive node (Fig. 2C). As they migrate into the streak and node, cells lose their attachment to the epiblast and form a new layer between the epiblast and hypoblast called the mesoderm (Fig. 2D). Thus, a middle, "icing" layer is created and the embryo becomes tri-laminar, like an oreo cookie with the icing (Fig. 2B). As cells detach from the streak and node, some remain in the icing layer and begin to migrate cranially and laterally to fill in this layer, while others integrate into the hypoblast, eventually replacing

this layer with a new set of cells derived from the epiblast (Fig. 2D). The new layers are generated in a cranial to caudal direction as the process of gastrulation continues through the 3rd and most of the 4th weeks. The top layer forms ectoderm, the middle layer forms mesoderm, and the bottom layer forms endoderm. Together the layers constitute the germ layers that will "germinate" all of the organs and tissues of the embryo.

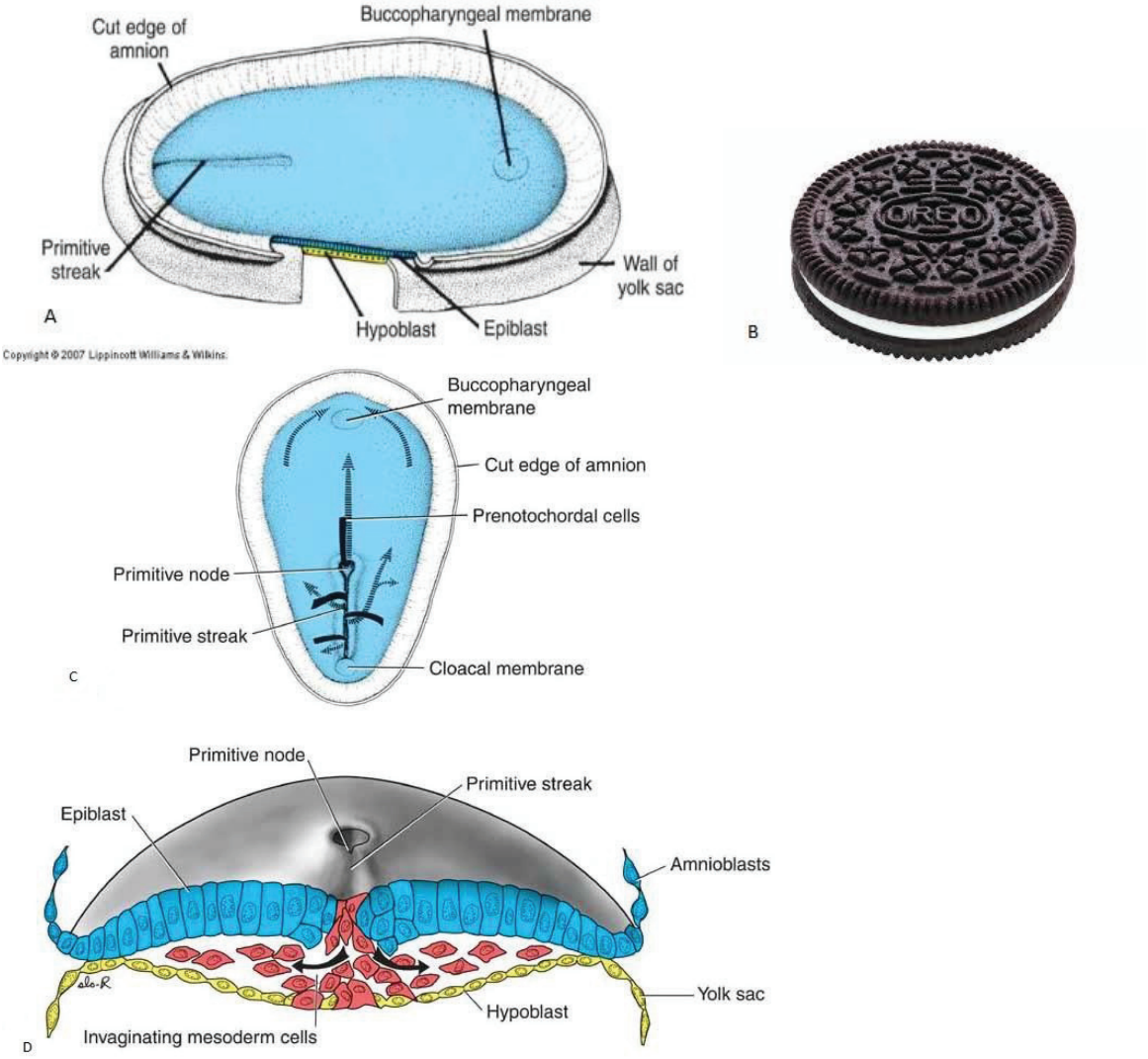


Figure 2A. Dorsal view of a 14 day embryo showing the epiblast (blue) with the primitive streak forming at the caudal end of the embryonic disc. **B.** Oreo cookie with icing. **C**. Dorsal view of a 16 day embryo undergoing the process of gastrulation whereby cells in the epiblast migrate toward the primitive streak and node, turn inward and continue their migration ventral to the epiblast layer. **D**. Cross section through the primitive streak of a 16 day embryo undergoing gastrulation. Epiblast cells (blue) migrate into the streak (brown cells), detach and then either form the middle ("icing") layer of the embryo or intercalate into the hypoblast layer and displace the hypoblast cells to form a new layer derived from the epiblast. The embryo now has 3 layers all derived from epiblast cells through

the process of gastrulation. Some epiblast cells remain in the top layer to form ectoderm, while the middle layer forms mesoderm, and the bottom layer forms endoderm. These 3 layers constitute the germ layers of the embryo and will form all of the tissues and organs.

Some of the first cells to migrate through the lateral edges of the node and upper region of the streak at 16-18 days post-conception are part of the mesoderm layer and form cardiac progenitor cells. These cells move cranially to a position cranial to the developing neural folds where they become organized into the Primary Heart Field (see arrows, Fig. 2C and primary heart field Fig. 3) (Sadler, '11; *Langman's Medical Embryology, 13th ed.*). As they migrate and arrive at this location, they are patterned from left to right on both sides of the neural plate as to their respective contributions to specific regions of the heart (Fig. 3; Abu-Issa and Kirby, '07). This patterning is dependent upon proper signaling through the laterality pathway regulated by 5-HT and, indeed, the heart exhibits more inherent laterality that most other structures, as indicated by its right and left chambers and the origin of its main blood vessels. Consequently, any disruption of this early patterning process, as is caused by Zoloft's and other SSRI's changing extracellular 5-HT concentrations and blocking 5-HT entering cells through SERT sites, alters L-R signaling, which can result in virtually every type of cardiac defect, including ASD, TAPVR, TGA, Dextrocardia, VSD, DORV, HPLV, HPRV, ventricular inversions and isomerisms, atrial isomerisms, and others. (See Table I, Section **VII**).

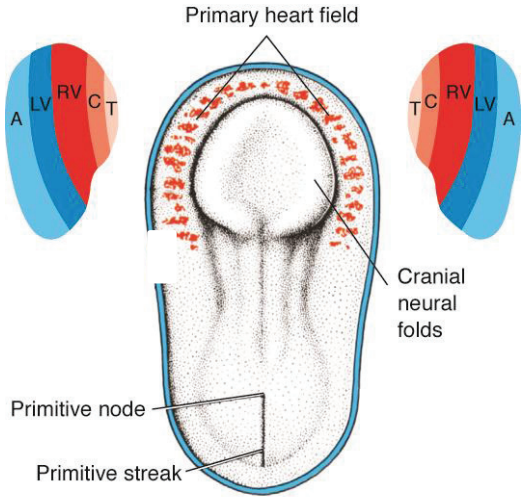


Figure 3. Cells from the epiblast migrate cranially to form the Primary Heart Field (PHF). As they migrate and arrive at their destination, they are patterned on each side into those that will form part of the right ventricle (RV); left ventricle (LV); and Atria (A). The outflow tract consisting of the conus cordis (C) and truncus areteriosus (T) as well as part of the RV will be formed from the secondary heart field (See text below)

The time frame when laterality and patterning are established is not the only period of susceptibility of the heart to insults by SSRIs, like Zoloft. Other stages in heart development are vulnerable because 5-HT acts as an important signaling molecule for critical processes in cardiac differentiation, including: (1) Lengthening the outflow tract via the secondary heart field (SHF); (2) Regulating neural crest cell (NCC) migration, proliferation, and apoptosis; (3) Septating the heart chambers by differentiation of endocardial cushions; and (4) Promoting growth and differentiation of myocardial cells (See Table 1).

A. Lengthening the outflow tract via the Secondary Heart Field (SHF) and regulating NCC migration, proliferation and apoptosis

After cardiac progenitor cells are patterned as the Primary Heart Field (PHF) during the 16^{th}-18^{th} days of gestation, they coalesce to form a horseshoe-shaped tube cranial to the neural plate. Then, as lateral body wall folding occurs, the two sides of the horseshoe are brought together in the midline where they fuse to form a single cardiac tube (Fig. 4). The caudal end of the tube represents the atrial region (red), the middle forms the left ventricular region (blue), and the cranial end forms the right ventricle and outflow tract (green and black). During the 23^{rd}-28^{th} days of gestation, looping of the heart tube occurs as the tube bends into the characteristically recognized shape of the heart (Fig. 4). While looping is occurring, the SHF, which forms as a collection of mesenchyme cells ventral to the floor of the pharynx, proliferates and lengthens the outflow tract of the heart tube (Fig. 5A). If this lengthening does not occur, multiple malformations of the heart and aortic arches are induced, including persistent truncus arteriosus, double outlet right ventricle (DORV), pulmonary stenosis, ventricular septal defects (VSDs), atrial septal defects (ASDs), tetralogy of Fallot, tricuspid atresia, interrupted aortic arch type B, right sided aortic arch, double aortic arch, and retroesophageal right subclavian artery (Yelbuz et al., 2002; Waldo et al., 2005; High et al., 2009). The process involved in lengthening the outflow tract is called convergent extension, whereby cells align themselves with a specific polarity, and it is regulated by the planar cell polarity pathway (PCP; Henderson et al.,'06; Phillips et al., '07; Henderson and Chaudhry, '11). This pathway is also involved in neurulation and gastrulation where it has been shown to be regulated by 5-HT and where disruptions in 5-HT concentrations and signaling cause neural tube defects and caudal dysgenesis (Colas et al., '99a,b; Colas and Schoenwolf, '01; Wang et al., '06; Schaerlinger et al., '07). Similar disruptions during

lengthening of the outflow tract of the heart result in DORV, VSDs, over-riding aorta, and interrupted aortic arch (Henderson et al., '06; Phillips et al., '07).

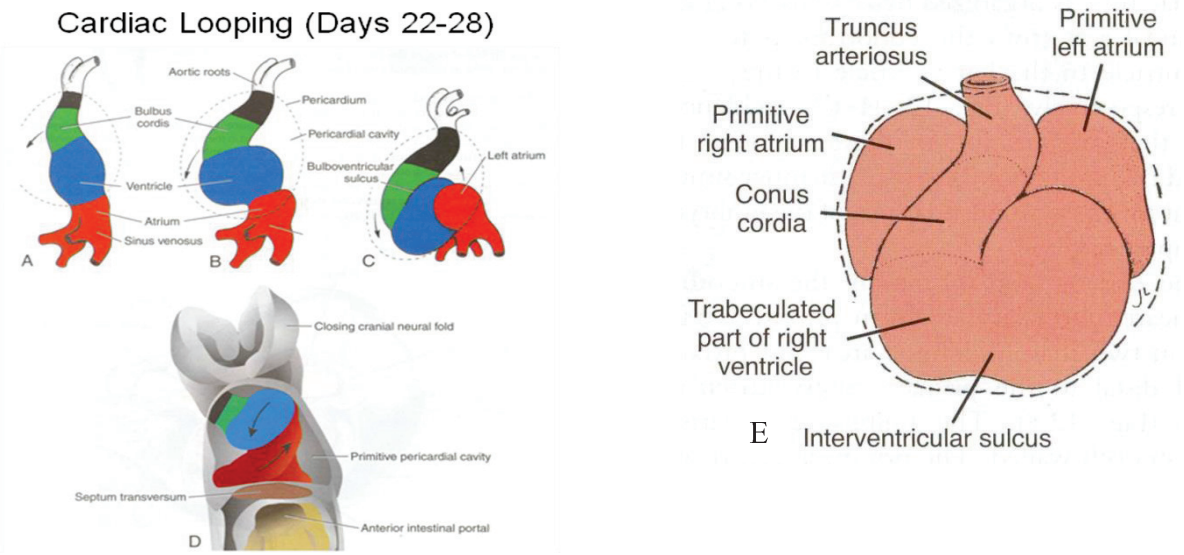


Figure 4. The heart tube is segregated into an atrial region (red), a ventricular region (blue), and an outflow tract region (green and black). Bending of the heart tube (looping; A-D) creates the recognizable shape of the heart (E). Lengthening of the black region of the heart is produced by the secondary heart field (SHF) in concert with cardiac neural crest cells (NCC) migrating to the heart from the cranial neural folds. (See Figure 4 A and B)

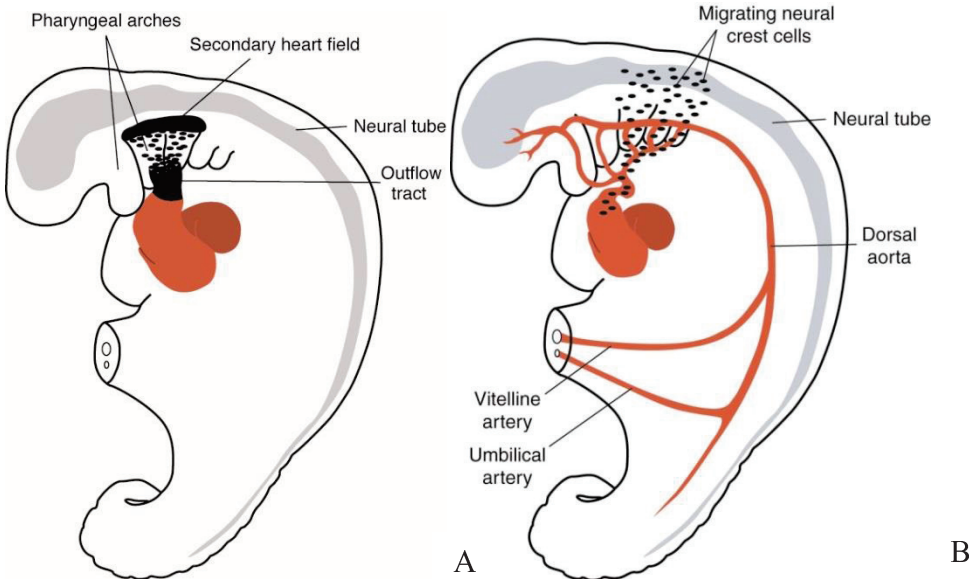


Figure 5. Cells forming in the secondary heart field (SHF) ventral to the pharynx lengthen the outflow tract region (A). Neural crest cells (NCC) migrate in close proximity to cells in the SHF (B) and the 2 cell populations work in concert through interacting signaling pathways to lengthen and septate the outflow tract.

Normal functioning of the SHF requires migrating cardiac neural crest cells (NCC). Thus, cells of the SHF and NCC interact through signaling pathways, resulting in lengthening of the outflow tract and in normal migration and patterning of NCC to populate endocardial cushions that septate the conus and truncus atriosus, i.e. the outflow tract, into the pulmonary artery and ascending aorta (Jiang et al., '00; Yelbuz et al., 02; Waldo et al., '05; High et al., '09). Each cell population requires the other to form and septate the outflow tract region (Waldo et al., 05; High et al., 09). NCC arise from neuroepithelial cells at the crests of the cranial neural folds, then migrate out of the folds down to the outflow tract region of the heart passing in close proximity to SHF cells (Fig.5B; Jiang et al., '00; Hutson and Kirby, '03). 5-HT is important for these processes because it acts as a signaling molecule regulating NCC migration (Moiseiwitsch and Lauder, '95) and proliferation and differentiation (Choi et al., '97). Therefore, a disruption of 5-HT concentrations, as is caused by SSRIs like Zoloft interferes with this signaling, which in turn, alters normal NCC differentiation, adversely affecting the SHF and resulting in the cardiac defects as described in detail above.

The vital role 5-HT plays in NCC development has been documented in the scientific literature. For example, physiological concentrations of 5-HT stimulate migration of isolated NCC in an in vitro assay, whereas migration was inhibited by treatment with 5-HT receptor antagonists (Moiseiwitsch and Lauder, 1995). Similarly, treatment of mouse embryos in embryo culture with an antagonist to the 5-HT2B receptor resulted in cardiac defects, inhibition of neural crest cell migration, and cell death in the crest cell population (Choi et al., '97). NCC express both the 5HT2B receptor and the 5-HT transporter, SERT, which provides an explanation for these observations (Choi et al., 1997; Hanson et al., 99). As noted previously, migration, proliferation, and differentiation of crest cells is essential for normal development of the conotruncal region of the heart. Therefore, any adverse effect on this cell population, as would occur with abnormal 5-HT concentrations produced by Zoloft, would result in outflow tract defects, including pulmonary stenosis, tetralogy of Fallot, transposition of the great vessels, and common truncus arteriosus.

In addition to interacting with the SHF, NCC are also directly involved in patterning the great arteries derived from the aortic arches. Inhibiting this regulation, as occurs from abnormal

concentrations of 5-HT produced by Zoloft, can result in abnormalities of these vessels, as described above (Kirby and Waldo, '95; Waldo et al., '96; Kirby, M.L., et al. 1997).

B. Septating the heart chambers by differentiation of endocardial cushions

Another target for SSRIs including Zoloft on heart development is endocardial cushion formation. Septum formation necessary to separate the heart into four chambers and the outflow tract into the pulmonary artery and the aorta, begins late in the 4th week of gestation and is completed by the 7th week. The key to normal septation are endocardial cushions that form in the region surrounding the atrioventricular canal and the outflow tract Fig.6). Initially, these cushions represent expansions of cardiac jelly (produced by myocardial cells) between the myocardium and endothelial lining of the heart tube. This expansion only occurs in the atrioventricular region and the outflow tract (Figs. 6-8). Cushion formation is induced by the myocardium and it is these cushions that will be essential for septation (Lockhart et al., '11; Sadler, '12).

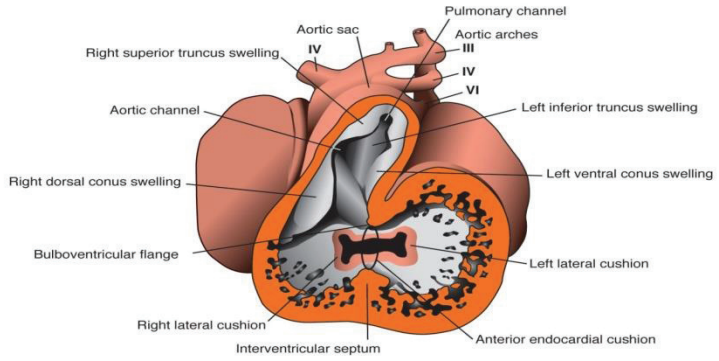


Figure 6. A. By 5 weeks endocardial cushions are present with 4 located around the atrioventricular canal (2 lateral, 1 anterior, and 1 posterior) and 4 in the outflow tract in the conus (right and left) and the truncus (right and left).

Following cushion formation by extracellular matrix deposition, additional signals from the myocardium, specifically in regions where the cushions develop, cause some of the endothelial cells lining the insides of the cushions to detach from their neighbors and transform into mesenchymal cells (Figs 7 and 8). Then, through cell migration, proliferation, and synthesis of additional extracellular matrix materials, these cells populate the cushions causing their continued growth (Figure 7: Eisenberg and Markwald, '95; Markwald et al., '96). A similar process occurs during cushion formation in the outflow tract (conus cordis and truncus

arteriosus), but cells populating those cushions are derived from NCC (Fig. 5B), not endocardial cells (Jiang et al., '00; Hutson and Kirby, '03).

Positioning of the outflow tract and AV cushions may be dependent upon 5-HT signaling in the precise regions where cushions will form. For example, at initial stages of heart tube formation and looping, 5-HT uptake sites appear throughout the myocardium (Figure 7A and 8A). During the later stages of looping, these uptake sites become localized to the AV canal and outflow tract (Figs. 7B and C and 8B) where endocardial cushions will form, indicating that 5-HT signaling is important for positioning the outflow tract cushions and forming the mitral and tricuspid valves that are derived from these structures (Shuey et al., '90; Yavarone et al., 93).

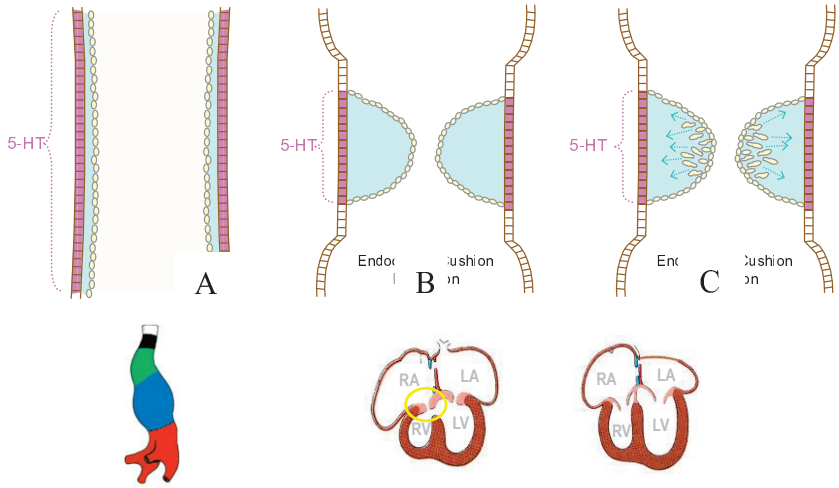


Figure 7. Formation of the endocardial cushions. **A.** Initially the heart tube consists of an external layer of cells called the myocardium, an inner layer called the endocardium, and a thin layer of extracellular matrix (blue). At this stage, all cells in the myocardium take up 5-HT. **B.** Cushions form in specific sites (atrioventricular canal and outflow tract) by increased synthesis of the extracellular matrix (blue). At this stage, 5-HT uptake by the myocardium is restricted to areas of cushion formation (pink). **C**. Eventually, cushions are populated by endocardial cells (in the atrioventricular canal) and by NCC (outflow tract) and these cells migrate toward the myocardial cells that take up 5-HT (pink) and 5-HT stimulates migration of these cells.

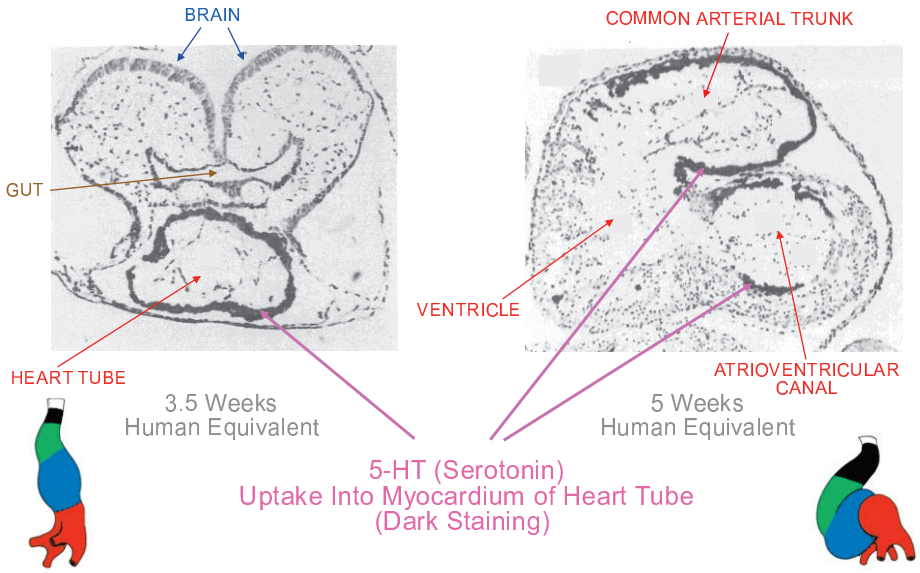


Figure 8. **A.** 5-HT (dark staining) uptake sites in the myocardium of a mouse heart at the tube stage of development (see Figure 6 A.). **B.** 5-HT uptake sites (dark staining) in the myocardium at a more advanced stage of development when endocardial cushions are forming in the atrioventicular canal and outflow tract (see Figure 6 A.).

As mentioned previously, endocardial cushions in the outflow tract depend upon NCC for their development. NCC originate from neuroepithelial cells at the edges (crests) of the neural folds as these folds elevate and fuse to form the neural tube. Cardiac neural crest cells form in the hindbrain region of the embryo in the 4th week and migrate ventrally toward the heart along three of the major branches (numbers III, IV, and VI) called the aortic arches, that connect the outflow tract with the dorsal aorta (Fig. 5 B). By the end of the 4th week, crest cells reach the heart to populate endocardial cushions in both regions of the outflow tract (called the conus cordis) and truncus arteriosus (Fig. 6; Jiang et al., '00; Hutson and Kirby, '03).

Four endocardial cushions form around the atrioventricular canal: two lateral, an anterior, and a posterior cushion (Fig.6). The anterior and posterior grow toward each other and fuse to separate the single atrioventricular canal into the right and left atrioventricular canals by the end of the 5th week (Fig. 6). In addition some of this cushion tissue proliferates to form the membranous portion of the interventricular septum, thereby completing formation of that septum. Later, the cushions surrounding both canals differentiate into the tricuspid valve on the right and the bicuspid (mitral) valve on the left.

In addition to its role in positioning the endocardial cushions, 5-HT signaling is involved in differentiation of the cushions. 5-HT binding protein, which regulates localized concentrations

of the neurotransmitter, is present in endocardial cushions during and after their formation (Yavarone et al., '93). Additionally, expression of the 5-HT2B receptor is localized to the myocardium before and after looping (Choi et al., '97). This receptor is coupled to the *ras* pathway that regulates cell proliferation (among other cellular phenomena; Lauder et al., '00). Proliferation and migration of endocardial cells in the AV canal cushions and NCC in the outflow tract cushions is essential for normal cushion differentiation. In the AV cushions, enodocardial cells break free from their neighbors and migrate toward myocardial cells that have taken up 5-HT (Figs. 7C and 8B; Eisenberg and Markwald, '95; Markwald et al., '96). Because 5-HT signaling has been shown to stimulate cell migration and proliferation in cardiac cells, it is likely that such signaling plays a key role in this process (Yavarone et al., '93; Choi et al., '97). It has also been shown that stimulation of migration in cushion mesenchyme cells by 5-HT was concentration dependent, such that concentrations that were too high or too low inhibited migration (Yavarone et al., '93). Thus, if 5-HT signaling is disrupted by abnormal concentrations of 5-HT as is caused by SSRIs including Zoloft, malformations of the AV valves would occur, including mitral insufficiency, tricuspid atresia, Ebstein's anomaly, and VSDs. Thus, the specificity of the localization of 5-HT uptake SERT sites and the presence of the 5-HT2B receptor and 5-HT binding protein suggest a critical role for serotonin in myocardial cell proliferation and differentiation and in endocardial cushion differentiation.

C. Promoting growth and differentiation of myocardial cells

As discussed above, uptake sites for 5-HT are present in myocardial cells that form the muscular tissue of the heart (Shuey et al., '90; Yavarone et al., '93). These cells also express the 5-HT transporter, SERT and the 5-HT2B receptor (Choi et al., '97: Sari and Zhou, '03). Studies have shown that 5-HT acts as a signaling molecule that increases proliferation in myocardial cells, whereas SSRIs like Zoloft inhibit their proliferation (Yavarone et al., 93; Sari and Zhou, '03). Furthermore, knocking out the 5-HT2B receptor causes neonatal death in mice due to severe ventricular hypoplasia caused by decreased proliferation of cardiac myocytes (Nebigil, et al., '00). Thus, the scientific literature indicates that heart defects such as hypoplastic left heart can be caused by SSRIs, including Zoloft.

Table 1. Summary of SSRI Targeted Tissues and the Resulting Heart Defects

Target Tissue	Cell Process	Normal Effect	Birth Defects
Primary* Heart Field (Days 16-18)	Establishment of laterality and patterning	Formation of the four chambered heart	DORV, TGA, l-TGA, ASD VSD, atrial isomerism ventricular inversion dextrocardia
Heart Tube* (Days 22-28)	Genetic signaling cascade for normal looping	Looping	dextrocardia
AVC* Endocardial Cushions (Days 26-35)	Cushion formation: cell proliferation and migration	Division of the AVC into left and right channels; Formation of the Mitral and tricuspid valves and the IVS	VSD, mitral and tricuspid valve defects (mitral insufficiency tricuspid atresia); positioning and leaflet defects
Secondary* Heart Field (Days 22-28)	Splanchnic mesoderm ventral to the pharynx and signaling from neural crest cells	Lengthening and partitioning the outflow tract into aortic and pulmonary channels	Tetralogy of Fallot TGA, Pulmonary atresia and stenosis
Outflow * Tract (Conotruncus) (Days 36-49)	Neural crest cell migration, proliferation and viability	Formation of the conotruncal cushions for division of the outflow tract	Common truncus arteriosus and other outflow tract defects
Aortic * Arches (Days 22-42)	Neural crest cell migration, proliferation and viability	Patterning the arches into the great arteries	Anomalous right pulmonary artery; IAA Type B

*Serotonin (5HT) can affect each of the target tissues.

Days give an approximate estimation of periods of vulnerability and are calculated from the time of fertilization.

Atrioventricular canal (AVC); Interventricular septum (IVS); Double outlet right ventricle (DORV); Transposition of the great arteries (TGA); left transposition of the great arteries (l-TGA); Atrial septal defect (ASD); Ventricular septal defect (VSD); Interrupted aortic arch (IAA).

D. Formation of the pulmonary veins and the origin of PAPVR and TAPVR

Formation of the pulmonary veins is dependent upon normal laterality signaling.

At approximately 22 days of gestation, the heart tube is suspended in the pericardial cavity by a double layered membrane called the dorsal mesocardium that extends from the gut tube to the heart tube (Fig. 9A and B). Most of this membrane breaks down except for small portions at the cranial and caudal poles of the heart tube. The caudal pole of the heart tube represents the primitive atrial region and at this location the dorsal mesocardium is continuous with another small proliferation of mesenchyme called the Dorsal Mesenchymal Protrusion (DMP). The DMP is derived from cells originating in the Secondary Heart Field (SHF) and it is in this structure that the pulmonary vein forms (Wessels et al., '00; Snarr, et al., '07a,b; Snarr et al., '08;

Bleyl et al., '10). Initially, the vein is a midline structure, but it will be re-positioned into the left atrium by growth of the inter-atrial septum. This septum forms from overlapping partitions that grow downward from the atrial roof (Figure 9B; Sadler, '13). The first partition is called the septum primum and it begins to grow from the roof of the common atrium (Fig. 9B). As the septum primum grows, the DMP containing the developing pulmonary vein grows with the septum primum and is positioned on the septum's left side (Fig. 9C; Bliss et al., '94; Wessels et al., '00; Blom et al., '01; Snarr, et al., '07a,b; Snarr et al., '08; Bleyl et al., '10). Continued growth of the septum positions the vein in the left atrium (Fig. 9C). Further expansion of the posterior atrial wall then incorporates more and more of the primary stem of the vein until its branches are reached and 4 separate openings, 1 for each of the 4 pulmonary veins, are present (Sadler, '13; Figure 9D).

Proper patterning of the atrial chambers, septum, and DMP occurs very early in development when laterality of the embryonic disc and the heart fields is established at 14-18 days of gestation (Nugent, '94; Martinez-Frias, '95; Gebbia et al., '97; Kosaki and Casey, '98; Ticho et al., '00; Morelli et al., '01; Bisgrove et al., '03; et al., '04; Ramsdell, '05; Abu-Issa and Kirby, '07; see also Section VII: Establishment of the Body Axes and Patterning in the Early Staged Embryo: Increased Sensitivity to SSRI (Zoloft)-Induced Teratogenesis). If the atrial septum does not grow normally or does not form in the proper position, then PAPVR or TAPVR occurs and the pulmonary veins may enter the right atrium or one of the other major veins in the area, such as the brachiocephalic vein or the superior vena cava. These abnormalities are accompanied by an atrial septal defect (ASD) because of the close association of the DMP, where the pulmonary vein forms, and the septum primum (Snarr et al., '07a,b). The fact that mice lacking expression of the laterality gene *PITX2* and that 70-80% of heterotaxy cases have TAPVR demonstrates that this anomaly is a laterality defect (van Mierop et al., '72; Kitamura et al., '99; Ware et al., '04).

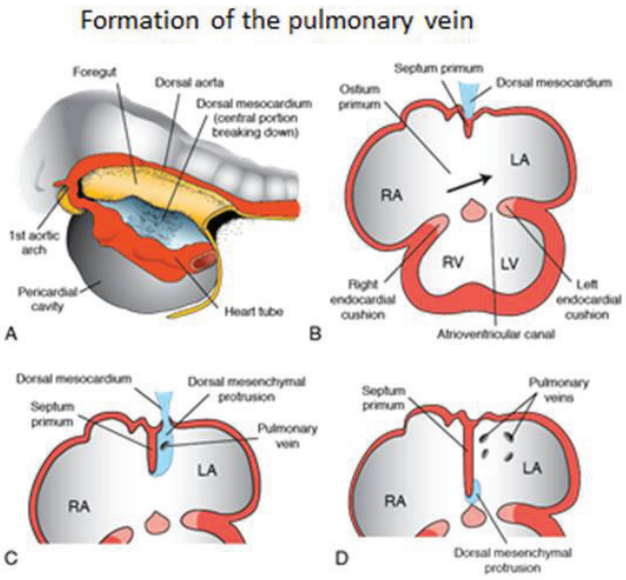


Figure 9. Formation of the pulmonary vein depends on asymmetry of the left-right axis during the establishment of laterality beginning at 14 days post conception. **A.** At 22 days the heart tube is suspended from the gut tube by a thin, double layered mesenchymal membrane (a mesentery) called the dorsal mesocardium. This mesentery is derived from the secondary heart field (SHF) and most of it disappears except for its cranial and caudal ends that contribute to heart development. **B.** Cross section through the heart at approximately 25 days showing the first part of the atrial septum called the septum primum forming in the roof of the common atrium near the attachment of the dorsal mesocardium. **C.** Cross section through the heart showing continued growth of the septum primum, which forms to the left of midline. As the septum grows a piece of the dorsal mesocardium called the dorsal mesenchymal protrusion (DMP), proliferates and becomes attached to the septum and it is in this tissue that the pulmonary vein forms. Because the septum primum forms to the left of midline and because the heart is patterned during the establishment of laterality and the process of gastrulation at 14-18 days of gestation, the pulmonary vein is directed into the left atrium. **D.** Continued expansion of the left atrium gradually incorporates more and more of the stem of the pulmonary vein until this expansion reaches the vein's 4 branches, thus accounting for the 4 venous openings into the definitive atrium.

IX. M[redacted] G[redacted]

I have reviewed medical records regarding Jessica Goulet including those documenting medication exposure during the first trimester and period of organogenesis of the heart, M[redacted]'s cardiac defects, and obstetric records involving Mrs. Goulet's pregnancy with M[redacted] and any risk factors for his cardiac defects which include [redacted] Medical records reflect an LMP of 11-20-03 and prescriptions of Zoloft prior to LMP on 10-23-03 and 11-14-03, and refills throughout the first trimester on 12-17-03, 1-16-04 and 2-14-04 (CVS pharmacy). In fact CVS records show continuation of the Zoloft throughout the pregnancy and into the post-partum period. Thus maternal exposure to Zoloft occurred throughout the pregnancy and during

the period of cardiac organogenesis when disruption of signaling by Zoloft could alter cardiovascular development and result in M[redacted]'s defects. I reviewed medical and pharmacy records for prescriptions filled during the first trimester and do not see exposure to other teratogens during the period of organogenesis. Prescription for Phenergan is noted 2/2/04 which is into her 11th week of gestation per LMP, outside the period of cardiac organogenesis. M[redacted] was born 8-20-04 birth by vaginal delivery at 39 weeks, 5 days gestation. Cord was 3 vessel. She was found to be cyanotic shortly following birth and diagnosed with congenital heart disease including [redacted] (operative report by Dr. John Mayer, Jr.. 8/24/04). M[redacted] underwent arterial switch operation on 8/24/04 during which time they performed suture closure of muscular [redacted] M[redacted]'s defects are consistent with disruption of laterality signaling as described above. OB records question mild mitral valve prolapse but the entry is scratched through and there is no evidence Mrs. Goulet has MVP. While maternal uncles reportedly were told they had murmurs none have ever been diagnosed with congenital heart disease. Thus family history is negative for diagnosed congenital heart disease per available medical records. Jessica Goulet was not reported to smoke or use alcohol or illicit drugs during the period of organogenesis. There is no evidence of maternal diabetes, obesity (BMI 26) or chronic medical condition that would increase the risk for congenital heart defects seen in this child. (Southern NHMC) Genetic testing (Microarray) collected on 11-19-13 and reported 11-26-13 was normal. I have considered all the embryologically relevant evidence regarding risk factors for M[redacted] G[redacted]'s congenital cardiac defects, including exposures during the period of cardiac patterning and development genetic testing, family history, and maternal medical history. I have considered all first trimester exposures, with a specific focus on exposures during the period of heart specification. Based on available evidence I have ruled out any exposures other than Zoloft as a cause of M[redacted] G[redacted]'s cardiac defects which include [redacted].

X. Summary of Opinions

In formulating my opinion in this case, I have gathered, reviewed, and considered the available literature, data, and resources reasonably utilized and relied upon by human embryologists and teratologists in the study of potential human teratogens. I have reviewed and analyzed available information regarding the association between first trimester exposure to Zoloft and birth defects and the exposures and risk factors in M[redacted] G[redacted]'s case. I have also

reviewed the relevant scientific literature on the role of serotonin in embryological development, particularly as this role relates to heart development. Based upon my knowledge, training, experience, and expertise in the fields of developmental biology, human embryology, teratology, and cardiac morphogenesis, and considering the totality of the evidence, it is my opinion to a reasonable degree of scientific probability that exposure to Zoloft during gestation at critical stages of embryogenesis can cause or substantially contribute to congenital heart defects, including [redacted] and did so in this child. M[redacted]'s defects are consistent with abnormal patterning of heart cells during the critical stage for laterality signaling, which is approximately days 14-18 of gestation. There are 3 critical periods when heart defects can be caused by Zoloft noting, however, that exposure prior to these critical windows can disrupt downstream signal disruption and cause or contribute to the formation of cardiac defects: 1) Days 14-18 when laterality is established and patterning of the primary heart cells occurs (with the caveat that there is scientific evidence that laterality may in fact commence earlier in gestation); 2) Days 23-28 when lengthening of the outflow tract occurs; 3) Weeks 4-8 when septation of the heart chambers and outflow tract occurs. Serotonin signaling is essential for establishing laterality when patterning of heart cells occurs and can be disrupted by SSRIs, including Zoloft. Mrs. Goulet was exposed to Zoloft throughout this critical period of heart development. The scientific literature clearly establishes roles for serotonin in establishing laterality, lengthening the outflow tract of the heart, and in differentiation of the endocardial cushions for septation of the heart and outflow tract, thereby demonstrating a biologically plausible mechanism of injury whereby Zoloft can cause adverse effects on embryogenesis of the heart and major vessels that result in birth defects in these structures.

The evidence supporting a teratogenic effect of Zoloft at this critical time period that could cause or substantially contribute to induction of heart and vascular defects is robust and compelling. The period of 14-18 days, when laterality signaling is occurring, is the time for induction of many different and complex heart malformations and there is compelling evidence that this is a critical time for SSRIs, including Zoloft, to disrupt embryogenesis and cause heart and vascular defects1) Animal models developed by Wilson ('53) and Monie ('66) prove that the sensitive period for disrupting laterality is at the primitive streak stage, approximately 14-18 days after fertilization. Just as importantly these studies showed that a variety of heart and great vessel defects, including ASDs, VSDs, hypoplastic left heart syndrome, dextrocardia, mitral and

tricuspid valve abnormalities, TGAs, pulmonary stenosis, hypoplastic right heart syndrome, DORV, common truncus arteriosus, ventricular inversions, failure of perforation of the atrial septum primum, common atrioventricular canal, TAPVR, and double aortic arch, could be induced at this "critical moment;" 2) Animal models clearly demonstrate that altering laterality signaling with SSRIs produce laterality defects. Furthermore, the timing for inducing such defects in chick embryos was at the primitive streak stage (Levin et al., '95; Fukumoto, '05a); 3) In mammals, disrupting signaling molecules involved in establishing laterality causes a wide variety of cardiac defects (Kathiriya and Srivastava, '00; Bamforth et al., '04; Ramsdell, '05; Ramsdell et al., '06); 4) Many clinical investigations of individuals and families with laterality (heterotaxy) defects demonstrate that malformations involving the heart are the most commonly observed abnormalities associated with laterality defects (Martinez-Frias, '95; Martinez-Frias et al., '95; Gebbia et al., '97; Kosaki and Casey, '98; Ticho et al., '00; Morelli et al., '01; Bisgrove et al., '03; Ware et al., '04) and that such defects may occur independently of any other evidence of a laterality defect (Morelli et al., '01; Bisgrove et al., '03; Ware et al., 04)

Finally, I considered the human epidemiologic evidence as I utilize it in my work as a human embryologist and teratologist. I considered studies which do not report an increased risk and those that do as well as information from other sources as cited on my reference list. As a human embryologist and teratologist there is a substantial amount of epidemiological evidence published in peer-reviewed journals which report an association between SSRIs in the first trimester and congenital defects of the heart and vasculature (Alwan et al., '07; Bar-Oz, '07; Louik et al., '07; Kallen and Olausson, '07; Merlob, '09; Pedersen, '09; Bakker et al., '10; Kornum, '10; Wurst et al., '10; Colvin, '11; Malm, '11; Jiminez-Solem, '12; Knudsen et al., '14; Ban, '14; Huybrechts, '14)

There is further substantial human epidemiologic evidence that **Zoloft** is associated with an increased risk of congenital cardiac defects with doubling and tripling of the risks of cardiac defects in infants exposed to Zoloft in the first trimester:

OR 2.0 (95% CI 1.2-4.0) for septal defects (**Louik et al,** *NEJM* 2007)
OR 3.25 (95% CI 1.21-8.75) for Septal heart defects (**Pedersen et al,** *BMJ* 2009
OR 3.0 (95% CI 1.4-6.4) for cardiac defects (**Kornum**/ *Clinical Epidemiology* 2010)
OR 3.3 (95% CI 1.5-7.5) for septal defects (**Kornum**/ *Clinical Epidemiology* 2010)
OR 3.08 (95% CI 1.45-6.55) for other congenital anomalies of heart (Colvin *Birth Defect Research, A* 2011)
OR 2.73 (1.75-4.26) for Congenital malformations of the heart(**Jiminez et al,** *British Medical Journal 2012)*
OR 3.60 (1.86-6.96) for Ventricular Septal Defects (**Jiminez et al,** *British Medical Journal 2012*
OR 3.09 (95% CI 1.82-5.25) for septal defects (**Jiminez et al,** *BMJ 2012)*
OR 2.85 (95% CI 1.35-5.99) for atrial septal defects (**Jiminez et al,** *BMJ 2012)*
RR 1.34 (1.02-1.76) for Atrial/ventricular septal defects (**Berard et al,** *AJOG (Jan. 2015)*

Thus, there is scientifically sound in vitro/in vivo animal data together with human clinical data to demonstrate to a reasonable degree of scientific probability that congenital heart and vascular malformations can result from exposure to Zoloft during critical periods of gestation.

Other organizations have stated sertraline and the SSRIs are teratogenic and increase the risk of cardiac defects. The American Heart Association listed SSRIs as "teratogens" in their 2014 paper regarding fetal echocardiography. The Canadian Therapeutics letter published February 2010 titled "Are antidepressants safe during pregnancy" states "a class effect is likely" and goes on to cite literature on sertraline (Zoloft) specifically and other SSRIs generally as associated with cardiac defects and spontaneous abortion. In the book Your Genes, Your Health by Dr. Aubrey Milunski, M.D., D.Sc. (2012) sertraline is listed in Table 23.1 titled "Medications Conclusively Shown to Cause Birth Defects" with "heart and other malformations" listed as the "Common Birth Defects and Consequences." The Center for Disease Control for the United States in a 2014 publication on medications in pregnancy "Treating for Two" states under the section on Antidepressants "A number of studies have identified some risks to the fetus and newborn associated with the use of antidepressant medications. Selective serotonin-reuptake inhibitors (SSRIs) are a frequently prescribed group of antidepressant medications. Several studies have shown an increased risk for heart defects associated with taking SSRIs during early pregnancy."

It is my opinion, rendered to a reasonable degree of scientific certainty that M[redacted] G[redacted]'s birth defects, [redacted], are due to exposure to Zoloft during the critical period of development when laterality signaling occurs. The defects are consistent with the fact that appropriate 5-HT concentrations are critical for regulating signals for establishing laterality and that the mechanism of action of SSRIs, including Zoloft, is to alter 5-HT concentrations in the extracellular space where signaling occurs. These alterations disrupt normal signaling by 5-HT and result in the types of birth defects present in M[redacted] G[redacted]. The fact that this child's Mother was taking Zoloft during the critical period when laterality signaling occurs and prior to this sensitive period of cardiac organogenesis, lack of family history of congenital cardiac abnormalities, lack of exposure to other teratogens during the period of cardiac development and the normal genetic testing results reinforces my opinion.

XI. Disclosures

The methodology and materials upon which I rely relied in formulating my opinions are generally accepted in the scientific community and are of the type, quality, and sources that others in my field of human embryology and teratology reasonably utilize and rely upon. My opinions contained herein are neither new nor novel. My opinions herein are expressed to a reasonable degree of scientific certainty and were formulated upon consideration of the totality of the evidence. I will testify at trial regarding the matters and opinions proffered in this report, as well as items reasonably related to the opinions contained in this report herein.

I reserve the right to alter or supplement my opinions. Additionally, I reserve the opportunity to testify in my areas of expertise in response to the testimony of Defendant's opinion witnesses. I am being compensated in connection with this matter at my customary rate of $500 per hour.

The following is a list of the cases in which, during the previous ten years, I testified as an expert witness at trial or by deposition.

Case:
Law firm: Phillips and Paolicelli, LLP
State: New York
Deposition: 2/28/13
Trial: N/A
Case resolution: Pending

Law firm: Robinson, Calcagnie, Robinson
State: New York
Deposition: 11/1/13
Trial: N/A
Case resolution: Pending

Law firm: Robinson, Calcagnie, Robinson
State: California
Deposition: 1/24 and 25/14
Trial: N/A
Case resolution: Pending

Law firm: Robinson, Calcagnie, Robinson
State: Philadelphia
Testified: 4/8/14
Daubert hearing:

Law firm: Robinson, Calcagnie, Robinson
State: California
Deposition: 2/2/15
Trial: N/A
Case resolution: Pending

Law firm: Blizzard Nabers
State: New Jersey
Deposition: 4/14/15
Trial: N/A
Case resolution: Pending

T.W. Sadler, PhD Date: 6/15/15

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